ESTUDIO DE FACTIBILIDAD TECNICO-FINANCIERA Y ECONOMICA PARA EL MONTAJE DE UNA PLANTA PRODUCTORA DE DEXTROSAS Y SIMILARES EN EL DEPARTAMENTO DE NARIÑO

(Tesis de Grado presentada como requisito parcial para optar al título de Economista)

Presidente de Tesis:

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Pasto, 1983

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GOFREY RIZO RIVAS

GUILLERMO MORENO OBANDO

UNIVERSIDAD DE NARIÑO

FACULTAD DE ECONOMIA

Pasto, 1983

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Ej. 1

A mi querida Esposa

AMPARO ZAMORA RODRIGUEZ

A mis Hijas:

MARIA DEL PILAR y

CLAUDIA PATRICIA

A todos mis Familiares

GOFREY RIZO RIVAS

30847

AGRADECIMIENTOS

Al Ingeniero Industrial EFRAIN CABRERA ZAMUDIO, actual Vicerrector Administrativo de la Universidad de Nariño y Director del presente Trabajo de Tesis de Grado, quien con su valiosa colaboración e indicaciones hizo que se culmine el presente trabajo.

A los profesores vinculados a la Facultad de Economía, quienes a lo largo de la carrera aportaron sus valiosos conocimientos.

A todas las personas que en una u otra forma colaboraron en la realización de la presente tesis.

A mi Padre,

ANGEL B. MORENO O.

A mi Madre,

ROSA M. OBANDO T.

A mi Esposa,

MARIA DOLORES SANTANDER

A mi Hijo,

GUILLERMO ANDRES

A todos mis Familiares

FRANCO GUILLERMO MORENO OBANDO

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A todas las personas que en una u otra forma colaboraron en la realización de la presente tesis.

TABLA DE CONTENIDO

"Las ideas y conclusiones aportadas en la tesis de grado son de responsabilidad exclusiva de sus autores".

Artículo lo. del Acuerdo No. 324 de 1966 (Octubre 11), emanado del Honorable Consejo Directivo de la Universidad de Nariño

TABLA DE CONTENIDO

	Pág.
INTRODUCCION	1
1. ESTUDIO DEL MERCADO	4
1.1. Demanda Global	4
1.2. Proyección de la Demanda	4
1.3. Distribución Geográfica de la Demanda	13
1.3.1. Pasto: Regional Central No. 1	15
1.3.2. Pasto: Regional No. 2	15
1.3.3. Regional Norte	15
1.3.4. Regional Sur	16
1.3.5. Regional Centro Occidental	16
1.3.6. Regional Occidente	16
1.3.7. Area de Penetración	17
1.4. Oferta	17
1.5. Determinación de Precios	20
1.6. Especificaciones de Productos y Uso	20
1.6.1. Grupo I: Dextrosas y Soluciones	20
1.6.2. Grupo II: Bicarbonatos y Electrolitos	21
1.6.3. Grupo III: Agua Estéril	22
1.7. Comercialización, Publicidad, Promoción, Otros	23
1.8. Conclusiones	25
2. DETERMINACION DEL TAMAÑO Y LOCALIZACION DE LA PLANTA	28

Pág.

2.1. Tamaño 28

2.1.1. Capacidad a Instalar 28

2.2. Disponibilidad de Materia Prima y Producción 31

2.3. Localización 34

2.3.1. Macrolocalización 34

2.3.1.1. Consumo 34

2.3.1.2. Facilidad de Servicios 36

2.3.1.3. Población 36

2.3.1.4. Vias de Comunicación 37

2.3.1.5. Telefonía 38

2.3.1.6. Puertos 42

2.3.1.7. Aeropuertos 42

2.3.2. Microlocalización 43

2.4. Conclusión 46

3. INGENIERIA DEL PROYECTO 47

3.1. Etapas Generales. Diseño del Proceso de Producción 48

3.1.1. Acondicionamiento del Agua 48

- Agua Potable 52

- Agua Blanda 53

- Agua Deionizada 54

- Agua para Inyección 55

3.1.2. Acondicionamiento de Reactivos 59

3.1.2.1. Reactivos Químicos Calidad USP. 59

Pág.

3.1.2.2. Productos Químicos Generales 62

3.1.3. Mezcla 62

3.1.4. Envasado 67

3.1.5. Esterilización 82

3.1.6. Inspección y Empaque 84

3.2. Distribución de la Planta 85

3.2.1. Area para Almacenamiento 86

3.2.2. Areas para Equipo 88

3.2.3. Areas para Administración de la Planta y Control de Calidad 91

3.2.4. Areas para Zonas Libres y Esparcimiento 92

3.3. Productos a Elaborar 96

3.4. Definición y Formulación Normalizada de Productos 98

3.4.1. Inyección de Dextrosa al 5% en Agua 98

3.4.2. Inyección de Dextrosa al 10% en Agua 99

3.4.3. Inyección de Dextrosa al 5% y Cloruro de Sodio al 0.9% en Agua 100

3.4.4. Inyección de Dextrosa al 5% y Cloruro de Sodio al 0.45% en Agua 101

3.4.5. Inyección de Cloruro de Sodio al 0.9% en Agua 103

3.4.6. Inyección de Ringer 104

3.4.7. Inyección de Hatman 105

3.4.8. Suero Fisiológico 107

3.4.9. Agua Estéril 108

Pág.

3.5. Requerimientos de Materia Prima e Insumos 108

3.5.1. Consumo de Agua en el Proceso 109

3.5.1.1. Equipo de Osmosis Inversa 110

3.5.2. Almacenamiento de Agua para Inyección 111

3.5.3. Almacenamiento de Agua Deionizada 115

3.5.4. Almacenamiento de Agua Blanda 116

3.5.5. Capacidad de Esterilización - Selección de Autoclaves

3.5.6. Selección de Caldera 119

3.5.7. Tanque de Almacenamiento de Combustible 119

3.5.8. Consumo de Agua para Enfriamiento Rápido de Esterilizador 120

3.5.9. Almacenamiento de Agua Potable Filtrada 121

3.6. Balance de Sólidos 122

3.7. Requerimientos de Reactivos Químicos 124

3.8. Requerimiento de Energía 125

4. INVERSIONES 127

4.1. Inversiones Fijas 127

4.1.1. Terrenos y Adecuaciones 127

4.1.2. Construcciones e Instalaciones 130

4.1.3. Maquinaria, Equipo y Dotación en General 130

4.1.4. Vehículos 130

4.2. Inversiones Diferidas 131

4.2.1. Instalación y Montaje de Equipo 131

Pág.

4.2.2. Puesta en Marcha y Organización 131

4.2.3. Imprevistos 131

4.2.4. Intereses durante la Construcción y el Montaje 132

4.3. Capital de Trabajo 132

4.3.1. Inventario de Materia Prima 132

4.3.2. Inventario de Productos Terminados 132

4.3.4. Inventario de Insumos 134

4.3.5. Gastos Generales 134

4.3.6. Imprevistos 134

4.3.7. Mano de Obra 135

4.4. Calendario de Inversiones 135

5. PRESUPUESTO DE INGRESOS Y EGRESOS 139

5.1. Ingresos 139

5.2. Egresos 139

5.2.1. Costos Directos de Producción 144

- Materia Prima 144

- Insumos 145

-- Envases de Vidrio 145

-- Tapones, Agrafes y Etiquetas 145

-- Empaques 145

-- Elementos Varios de Consumo 145

- Mano de Obra Directa 146

- Agua Potable 146

Pág.

- Energía Eléctrica 146
- Combustibles 147
- Gastos Generales de Producción 147
-- Mano de Obra Indirecta 147
-- Seguros de Maquinaria y Equipo 147
-- Seguros de Construcciones 147
-- Depreciación 148
- Gastos de Administración 148
-- Sueldos Personal Administrativo 148
-- Agua y Energía 148
-- Suministros de Oficinas 148
-- Combustible para vehículos 149
- Gastos Financieros 149
- Gastos Diferidos 149

5.3. Punto de Nivelación 149

6. FINANCIAMIENTO 154

6.1. Alternativa 1 158

6.2. Alternativa 2 158

6.3. Líneas de Financiación 158

6.4. Capacidad de Pago 160

6.5. Estados Financieros Proforma 164

6.5.1. Estado de Pérdidas y Ganancias 164

6.5.2. Balances 170

Pág.

7. ORGANIZACION 173

7.1. Asamblea General de Socios 175

7.2. Junta Directiva 175

7.3. Revisor Fiscal 176

7.4. Gerencia 177

7.5. Departamento de Producción 177

7.6. Departamento de Control de Calidad 178

7.7. Departamento Administrativo 178

7.7.1. Unidad de Contabilidad y Finanzas 178

7.7.2. Unidad de Almacén y Ventas 179

7.7.3. Unidad de Servicios Generales 179

7.7.4. Unidad de Personal 180

8. EVALUACION 181

8.1. Evaluación Privada 181

8.1.1. Tasa Interna de Retorno TIR 181

8.1.2. Tasa Interna de Retorno Financiero 182

- Para la Empresa 182

- Para el Empresario 182

8.2. Análisis de Sensibilidad 182

8.3. Evaluación Social 183

CONCLUSIONES Y RECOMENDACIONES 190

BIBLIOGRAFIA 194

ANEXOS

LISTA DE CUADROS

Cuadro 1 DEMANDA DE LOS PRODUCTOS EN ESTUDIO DE LOS AÑOS 1977-1981

Cuadro 2 PROYECCION DE LA DEMANDA. GRUPO DE DEXTROSAS Y SOLUCIONES FCO. DE 500 cc.

Cuadro 3 PROYECCION DE LA DEMANDA. GRUPO DE BICARBONATOS. FCO. POR 10 cc.

Cuadro 4 PROYECCION DE LA DEMANDA DE AGUA ESTERIL. AMPOLLA POR 1 cc.

Cuadro 5 PROYECCION DE LA DEMANDA Y REDUCCION A UNIDAD DE MEDIDA. 1985-1994

Cuadro 6 TAMAÑO DEL PROYECTO EN BASE A LA DEMANDA

Cuadro 7 CAPACIDAD CAMAS INSTALADAS EN EL DEPARTAMENTO. 1980

Cuadro 8 POBLACION ESTIMADA PARA EL DEPARTAMENTO DE NARIÑO. 1981

Cuadro 9 DISTANCIAS ENTRE PASTO Y LOS HOSPITALES DEL DEPARTAMENTO

Cuadro 10 INFRAESTRUCTURA BASICA DE LOS SECTORES SELECCIONADOS PARA LA MICROLOCALIZACION

Cuadro 11 SOLUBILIDAD EN AGUA A 20°C

Cuadro 12 PARTICIPACION PORCENTUAL DE PRODUCTO OBSERVADO EN 1981 Y PROYECCION DEMANDA PARA 1985

Cuadro 13 INVERSIONES FIJAS Y DIFERIDAS EN EL PROYECTO

Cuadro 14 CAPITAL DE TRABAJO

Cuadro 15 CALENDARIO DE INVERSIONES

Cuadro 16 LISTA DE PRECIOS MAXIMOS AL PUBLICO, VIGENTES PARA 1983

Cuadro 17 PRESUPUESTO ANUAL DE INGRESOS 1985-1994

Cuadro 18 PRESUPUESTO ANUAL DE EGRESOS 1985-1994

Cuadro 19 COSTOS FIJOS Y VARIABLES AL 100% DE PRODUCCION

Cuadro 20 CALCULO DE PUNTO DE NIVELACION AL 100%

Cuadro 21 ESTRUCTURA FINANCIERA DE LA PLANTA

Cuadro 22 APORTACION SOCIOS DE ACUERDO A PRESUPUESTO 1983

Cuadro 23 PLAZOS E INTERESES DE FINANCIACION

Cuadro 24 TABLA DE AMORTIZACION E INTERESES

Cuadro 25 FLUJOS DE CAJA PROYECTADOS 1984-1994

Cuadro 26 ESTADO DE PERDIDAS Y GANANCIAS PROYECTADO 1985-1994

Cuadro 27 BALANCE PROYECTADO 1985-1994

Cuadro 28 CAPITAL DE TRABAJO 1985-1994

Cuadro 29 DEPRECIACIONES 1985-1994

Cuadro 30 CESANTIAS CONSOLIDADAS 1985-1994

Cuadro 31 TASA INTERNA DE RETORNO DEL PROYECTO

Cuadro 32 TASA INTERNA DE RETORNO FINANCIERO PARA LA EMPRESA

Cuadro 33 TASA INTERNA DE RETORNO FINANCIERO PARA EL EMPRESARIO

Cuadro 34 ANALISIS DE SENSIBILIDAD CONSIDERANDO AUMENTO Y DISMINUCION EN LAS INVERSIONES FIJAS

Cuadro 35 ANALISIS DE SENSIBILIDAD CONSIDERANDO AUMENTOS Y DISMINUCIONES EN LAS VENTAS

Cuadro 36 TASA INTERNA DE RETORNO ECONOMICO TIRE.

LISTA DE GRAFICOS

Gráfico 1 CONSUMO OBSERVADO GRUPO DE DEXTROSAS 1977-1981

Gráfico 2 CONSUMO OBSERVADO GRUPO DE BICARBONATOS 1977-1981

Gráfico 3 CONSUMO OBSERVADO GRUPO DE AGUA ESTERIL 1977-1981

Gráfico 4 CRONOGRAMA DE DESARROLLO DEL PROYECTO

Gráfico 5 PUNTO DE NIVELACION

Gráfico 6 ORGANIGRAMA

LISTA DE PLANOS

Plano 1 DISTRIBUCION AREA ESTERIL

Plano 2 DISTRIBUCION AREA ASEPTICA

Plano 3 DISTRIBUCION GENERAL DE LA PLANTA FISICA

LISTA DE MAPAS

Mapa 1	DEPARTAMENTO DE NARIÑO. RECURSO INSTITUCIONAL DE SALUD
Mapa 2	DEPARTAMENTO DE NARIÑO. CROQUIS DE RUTAS

LISTA DE DIAGRAMAS

Diagrama 1	PLANTA PRODUCTORA DE DEXTROSAS Y ELECTROLITOS. CANALES UTILIZADOS EN LA COMERCIALIZACION
Diagrama 2	ESQUEMA SIMPLIFICADO DEL PROYECTO
Diagrama 3	ACONDICIONAMIENTO DE AGUA
Diagrama 4	ACONDICIONAMIENTO DE REACTIVOS
Diagrama 5	MEZCLA DE SOLUCIONES
Diagrama 6	ENVASADO Y ESTERILIZACION DE PRODUCTOS
Diagrama 7	PROCESO DE LAVADO DE ENVASES
Diagrama 8	PROCESO DE PRODUCCION

LISTA DE ANEXOS

Anexo 1 CALCULOS PARA PROYECCION DE LA DEMANDA

Anexo 2 NORMAS FARMACOPEA USP.

Anexo 3 INVERSION EN EQUIPOS Y DOTACION GENERAL

Anexo 4 REQUERIMIENTOS DE PERSONAL

Anexo 5 ENCUESTA A HOSPITALES

INTRODUCCION

"Los proyectos bien estudiados y bien hechos podrán contribuir a despertar el interés por desarrollarlos y tendrán más probabilidad de atraer la atención de los posibles ejecutores justamente en la medida que hayan sido bien elaborados y presentados". 1/

La nueva unidad productora de Dextrosas y Similares, materia del presente estudio, se utiliza para elaborar medicamentos de uso médico y se emplea para restablecer el equilibrio líquido del organismo humano. Como es de conocimiento general, la salud como función del estado debe brindarse a toda la población sin ninguna distinción de riqueza, religión, raza o credo. Dentro de los lineamientos políticos nacionales debe incluirse en la programación de servicios las áreas periféricas y las zonas urbanas con el propósito de integración.

En la actualidad estos productos son adquiridos en el interior del pais lo que hace que el producto sufra un costo adicional de transporte.

1/ Manual de Proyectos de Desarrollo Económico de las Naciones Unidas - ONU. 1972.

La tasa de crecimiento poblacional para 1964-1973 en una cifra de 2.6 indica un elevado crecimiento de demanda de servicios y obviamente la demanda de productos se presenta en forma creciente en las entidades de salud, debido al incremento demográfico; mientras que por otra parte los recursos financieros son cada vez mas escasos y no alcanzan a cubrir la demanda de servicios de la población colombiana. Esto puede corroborarse con la composición porcentual del presupuesto nacional, que en el año de 1974 el sector Salud participaba del 8.85% y en 1979 esta cifra bajó al 6.87%, lo que permite apreciar que el sector representa cada vez una proporción mas pequeña del presupuesto nacional y está perdiendo importancia frente a otras entidades del estado colombiano, como Defensa Nacional que en 1974 constituía el 13.53% y pasó en 1979 al 15.23%.

Para determinar la cantidad demandada de los productos objeto del presente estudio se realizaron encuestas que cubren el total del universo hospitalario en el Departamento de Nariño.

Se toma como base la demanda histórica de 5 años, comprendidos entre 1977 y 1981. Una vez determinada la tendencia se proyecta para una vida útil de 10 años.

La encuesta se diseña para obtener información del consumo de 22 productos, que a su vez se agrupan en tres grandes categorías en atención

a sus características de producción, presentación y uso, estos grupos son:

Dextrosas y Soluciones	Frascos por 500 cc
Bicarbonatos	Frascos por 10 cc
Agua Estéril	Frascos por 1 cc

Se inicia con el estudio de mercado que es la base fundamental para seguir adelante en el presente proyecto y, en el cual los procesos particulares se trabajan uno a uno hasta obtener el conjunto global.

El establecimiento de esta Planta Productora de Dextrosas y Similares tiene gran perspectiva al constituirse como una empresa comercializadora del estado, garantizando su funcionamiento puesto que tiene un mercado seguro, es decir se crea una empresa con características monopolísticas. Con el propósito que el servicio seccional de salud tenga una fuente financiera propia, además de una entrega oportuna de medicamentos se persigue con este trabajo contribuir a mejorar la situación financiera de la seccional de salud, así como también a contribuir con el desarrollo de la industria en el Departamento, buscar la descentralización de la producción y minimizar costos.

Se considera además que si se emprende iniciativas de este tipo con una mediana capacidad de empleo se estará dando soluciones para salir de las condiciones de atraso, pobreza y desempleo que agobian al Departamento y principalmente su capital: Pasto.

CAPITULO I

ESTUDIO DE MERCADO

1.1. Demanda Global

Los resultados de la demanda en los 13 Hospitales del Departamento mas la Clínica del Seguro Social se puede ver en el Cuadro 1, que trata sobre la demanda observada de los productos en estudio durante los años 1977 a 1981.

Para mayor ilustración se presentan 3 gráficos que representan el consumo observado en los 5 años de estudio y corresponden al Grupo de DEXTROSAS, BICARBONATOS y AGUA ESTERIL.

1.2. Proyección de la Demanda

Para proyectar la demanda futura los resultados se procesaron con el objeto de buscar el modelo matemático que mejor se acomode a los datos observados.

Se analizaron tres modelos matemáticos para observar el comportamiento de consumo en los 5 años que se toman como base, ellos son:

Ecuación Línea Recta $y = a + bx$

Gráfica. : 1

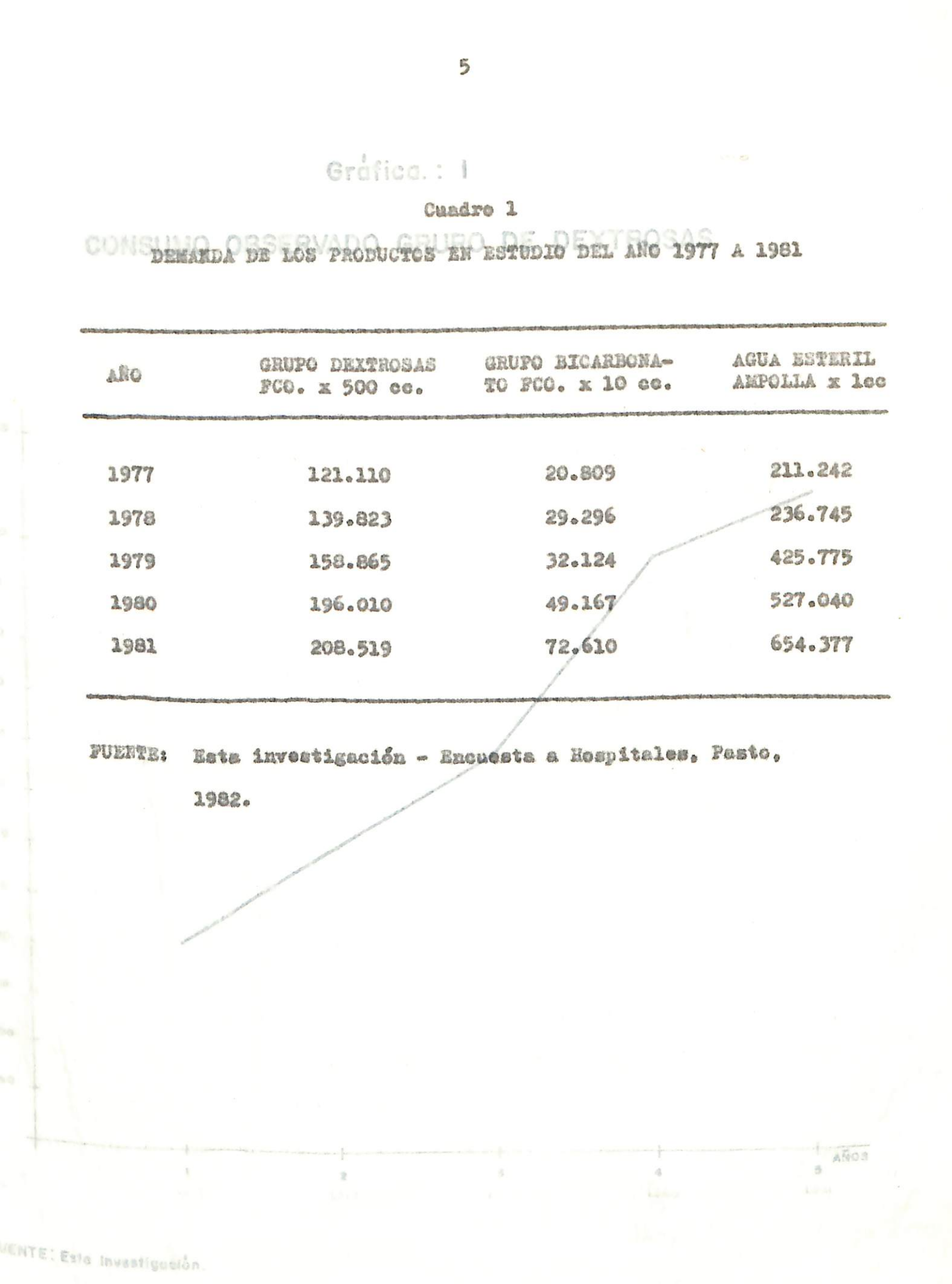
Cuadro 1

CONSUMO OBSERVADO GRUPO DE DEXTROSAS

DEMANDA DE LOS PRODUCTOS EN ESTUDIO DEL AÑO 1977 A 1981

AÑO	GRUPO DEXTROSAS FCO. x 500 cc.	GRUPO BICARBONATO FCO. x 10 cc.	AGUA ESTERIL AMPOLLA x 1cc
1977	121.110	20.809	211.242
1978	139.823	29.296	236.745
1979	158.865	32.124	425.775
1980	196.010	49.167	527.040
1981	208.519	72.610	654.377

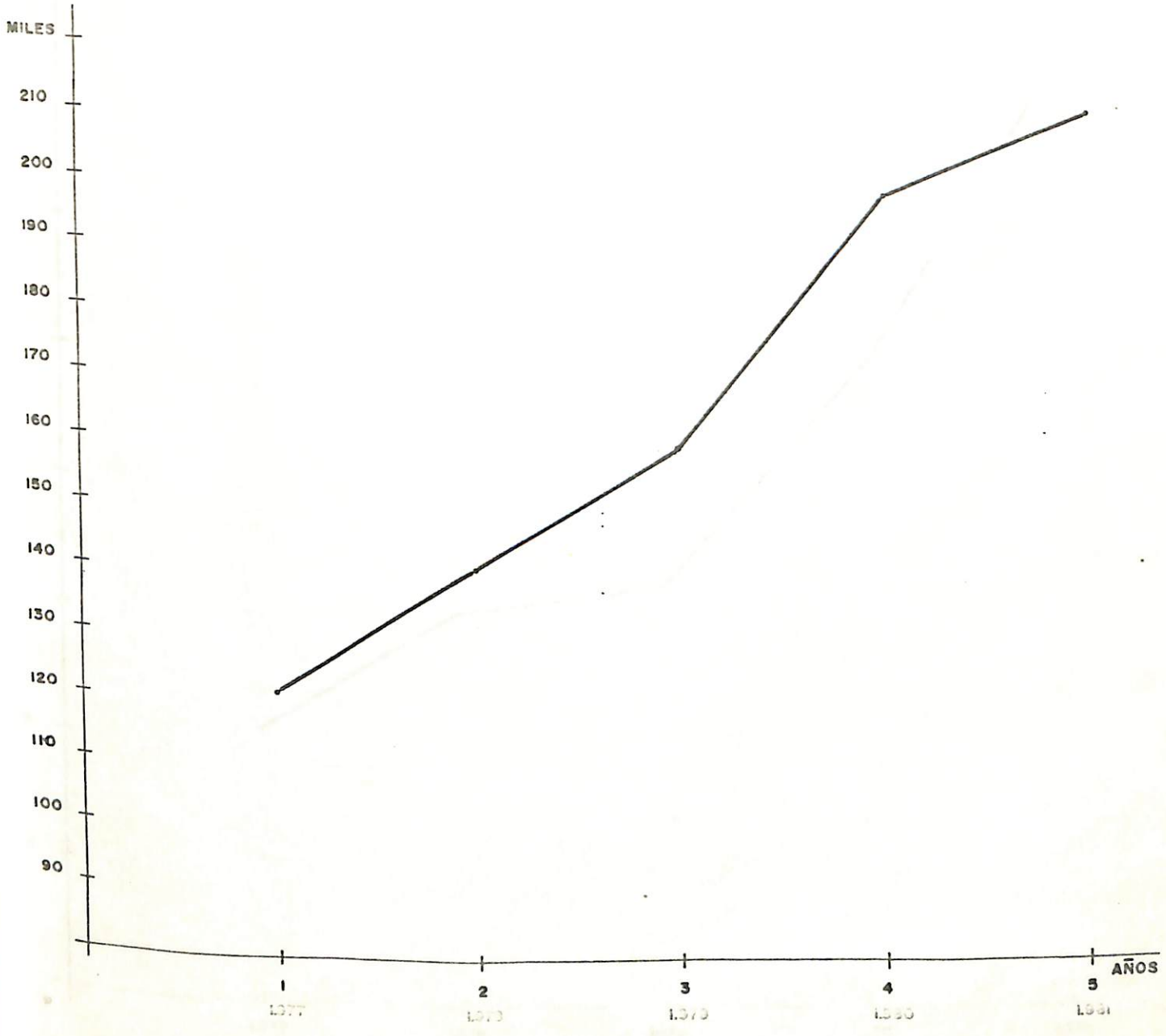
FUENTE: Esta investigación - Encuesta a Hospitales, Pasto, 1982.



FUENTE: Esta investigación.

Gráfica. : 1

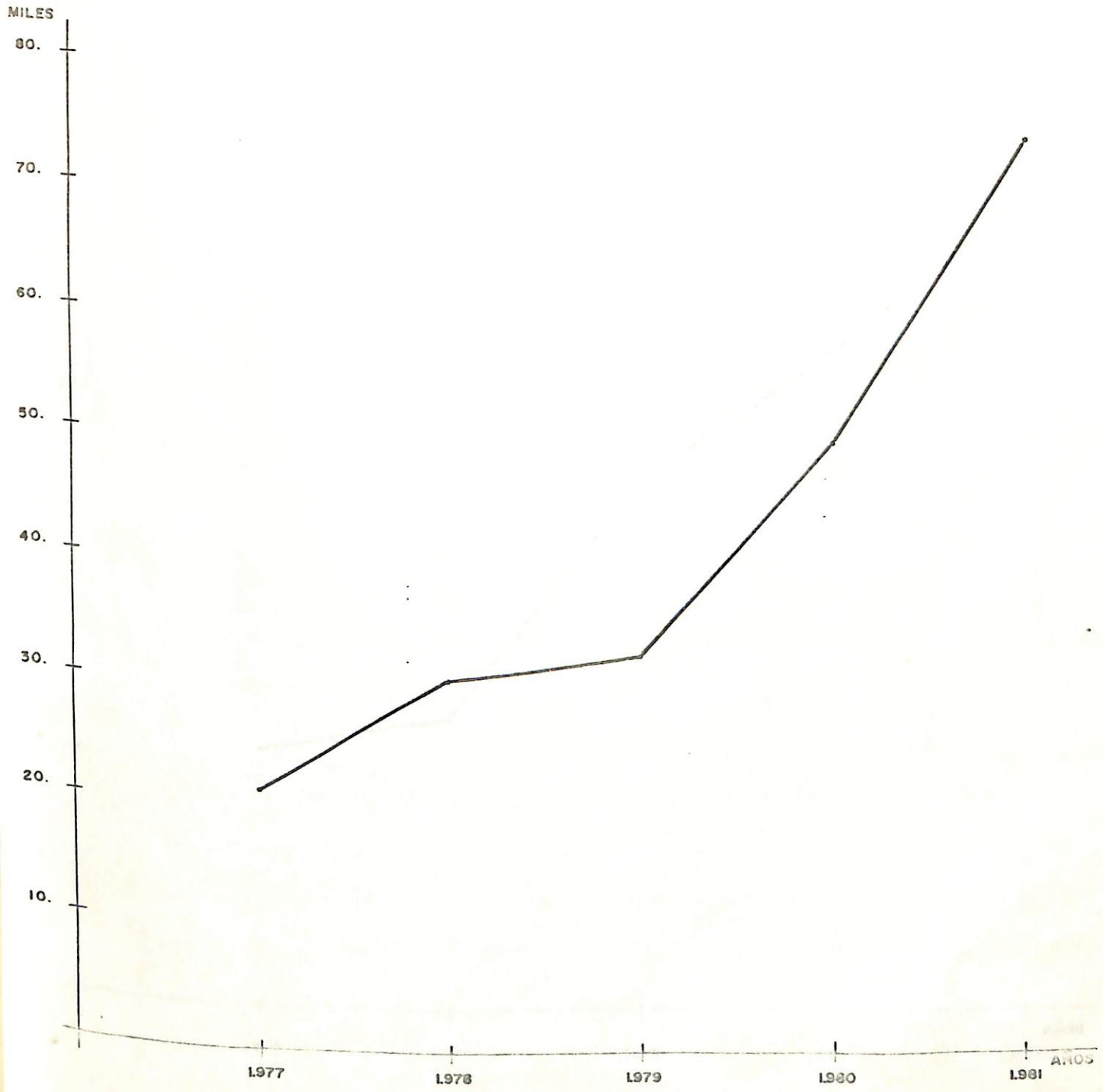
CONSUMO OBSERVADO GRUPO DE DEXTROSAS



FUENTE: Esta investigación.

Gráfica. : 2

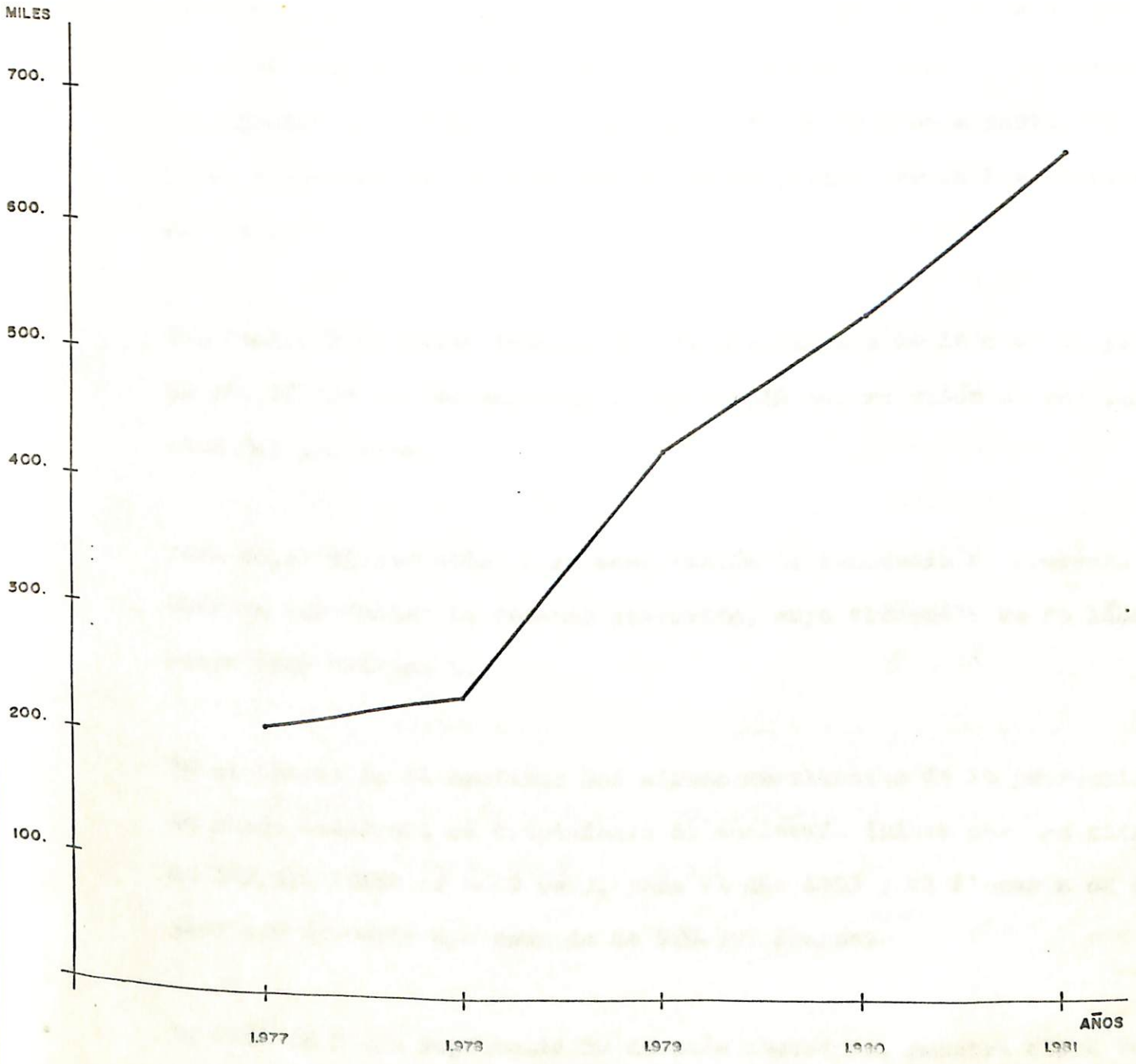
CONSUMO OBSERVADO GRUPO BICARBONATOS



FUENTE: Esta Investigación.

Gráfica. : 3

CONSUMO OBSERVADO GRUPO AGUA ESTERIL



FUENTE: Esta Investigación.

Ecuación Parabólica $y = a + bx + cx^2$

Ecuación Exponencial $y = a \cdot b^x$

El procedimiento de cálculos se puede apreciar en el Anexo 1.

Estos modelos fueron aplicados para los tres grupos y en cada uno de ellos se seleccionó el que menor error típico presentó y se procedió a proyectar la demanda para una vida útil de 10 años a partir de 1985, obteniéndose los resultados que se pueden ver en los Cuadros 2, 3 y 4.

Del Cuadro 2 se puede deducir que el crecimiento de la demanda para el año décimo es incrementado en un 68.51% con relación al año inicial del proyecto.

Para mayor ilustración en la observación de tendencia se presenta una Gráfica que indica la demanda observada, cuya tendencia es de línea recta (ver Gráfica 1).

En el Cuadro 3, al analizar las cifras resultantes de la proyección se puede decir que su crecimiento es acelerado inicia con una cifra de 222.051 (frascos x 10 cc.), para el año 1985 y al llegar a su décimo año presenta una demanda de 928.902 frascos.

La Gráfica 2 que representa la demanda observada, muestra clara ten-

Cuadro 2

PROYECCION DE LA DEMANDA GRUPO DEXTROSAS Y SOLUCIONES

FCO. x 500 cc.

AÑO	Y = DEMANDA FUTURA
1985	303.471
1986	326.572
1987	349.673
1988	372.774
1989	395.875
1990	418.976
1991	442.077
1992	465.178
1993	488.279
1994	511.380

FUENTE: Cálculo elaborado por autores de la presente tesis según Anexo 1.

Cuadro 3

PROYECCION DE LA DEMANDA DEL GRUPO BICARBONATO

PCO. x 10 cc.

AÑO	Y = DEMANDA FUTURA
1985	222.051
1986	275.374
1987	335.001
1988	400.932
1989	473.167
1990	551.706
1991	636.549
1992	727.696
1993	825.147
1994	928.902

FUENTE: Cálculo elaborado por autores de la presente tesis según Anexo 1.

Cuadro 4

PROYECCION DE LA DEMANDA DE AGUA ESTERIL

AMPOLLA x 1 cc.

AÑO	Y = DEMANDA FUTURA
1985	1'116.975
1986	1'234.631
1987	1'352288
1988	1'469.945
1989	1'587.601
1990	1'705.258
1991	1'822.914
1992	1'940.571
1993	2'058.227
1994	2'175.883

FUENTE: Cálculo elaborado por autores de la presente tesis, según Anexo 1.

dencia de curva parabólica.

Los datos del Cuadro 4 indican su crecimiento al comparar los años 1985 con 1994.

La Gráfica 3 representa los datos observados con una tendencia de línea recta aritmética.

Los productos en estudio presentan una demanda inelástica; el cambio en los precios no afecta su consumo, porque se trata de medicamentos indispensables en las entidades hospitalarias y que independientemente de su precio deben existir en cantidades suficientes para atender los problemas de salud que requieren estos productos.

1.3. Distribución Geográfica de la Demanda

El Servicio Seccional de Salud de Nariño, cuenta con un total de 123 establecimientos distribuidos en la siguiente forma: 13 hospitales, 21 centros de salud y 89 puestos de salud. Su distribución geográfica puede verse en el Mapa 1.

De acuerdo con la subdivisión realizada por el grupo de ordenamiento urbano en el Departamento de Nariño se presenta la siguiente situación en términos de regionalización. 1/

1/ PLANEACION NACIONAL. Estudio Fronterizo Nariño-Putumayo.

MAPA. : I

DEPARTAMENTO DE NARIÑO

RECURSO INSTITUCIONAL

FUENTE: Anuario Estadístico Servisalud Nariño, año 1.980

1.3.1. Pasto: Regional Central No. 1

Aquí funcionan dos hospitales y 17 puestos y Centros de Salud. Según el cálculo de población para 1981, la población a atender por esta regional se estimó en 163.936 habitantes. Está conformada por los siguientes municipios: Pasto, Funes, Tangua, Buesaco, Consacá, El Tablón y Yacuanquer.

1.3.2. Pasto: Regional No. 2

La sede de esta regional en el Hospital San Pedro, cuenta además con un hospital local en el Municipio de Sandoná, 3 Centros de Salud y 11 Puestos de Salud. Su conformación agrupa los municipios de Pasto, Sandoná, Ancuya, Linares, El Tambo, La Florida. Su población asignada es de 186.673 habitantes.

1.3.3. Regional Norte

Esta regional tiene su central en el Hospital Eduardo Santos de la Unión, existen en total 21 establecimientos. Este subsistema está formado por los Municipios de La Unión, La Cruz, San Lorenzo, San Pablo, Berruecos, Colón, Génova, Taminango y San José de Albán. Su población calculada es de 126.360 habitantes.

1.3.4. Regional Sur

La regional Sur del Departamento tiene su sede en Ipiales Hospital San Vicente, cuenta con un total de 20 establecimientos, 7 centros de salud, 12 puestos de salud y un hospital; la conforman los municipios de Ipiales, Pupiales, Contadero, Guachucal, Cumbal, Gualmatán, Córdoba, Aldana, Puerres, Potosí, Iles, Cuaspud. Su población es de 175.474 habitantes.

1.3.5. Regional Centro Occidental

Tiene su sede en el Hospital San José en el Municipio de Túquerres y la integran los municipios de Sotomayor, Santa Cruz, Guaitarilla, Sameniego, Ospina, Sapuyes, Imués, Ricaurte, Piedrancha. El cálculo de su población por zonas urbanas y rurales es de 137.248 para el año de 1981. El subsistema en su conjunto cuenta con 17 establecimientos. Existiendo dos hospitales, un centro de salud y 14 puestos de salud.

1.3.6. Regional Occidental

El Hospital San Andrés de Tumaco es la sede de la regional occidental, que en total cuenta con 23 establecimientos de salud, de ellos dos hospitales locales y un hospital regional; son además 20 puestos

de salud. Seis municipios integran esta regional y son: Tumaco, Barbacoas, El Charco, Roberto Payán, Maguí, Mosquera. Su población proyectada para atender en 1981 fue de 218.558 habitantes.

1.3.7. Area de Penetración

En esta zona existen únicamente 7 organismos de salud, un centro hospitalario y 6 puestos de salud, como puede analizarse no hay un solo hospital en la región. Su población calculada es de 42.240 habitantes y forman parte de ella los municipios de Cumbitara, El Rosario, Policarpa y Leiva.

Los mayores porcentajes en cuanto a establecimientos de salud se localizan en Pasto, que cuenta con dos regionales (29%), Tumaco (19%) y La Unión (17.35%). El cálculo de población por zonas urbanas y rurales y por grupos de edades en el Departamento de Nariño para el año de 1981 correspondió a la cifra de 1'050.489 habitantes.

1.4. Oferta

La oferta de los productos en estudio la representan diferentes laboratorios productores de droga ubicados en el interior del país, entre los mas importantes se destacan:

NOMBRE	LOCALIZACION
Laboratorios Quibi	Bogotá
Laboratorios Travenol	Bogotá
Laboratorios Ecar	Bogotá
Laboratorios Junín	Medellín

Estos laboratorios son de origen privado, actualmente abastecen toda la demanda del mercado, son empresas de una trayectoria apreciable en el mercado nacional y por la calidad de sus productos se puede deducir que su tecnología es bastante desarrollada.

Para realizar un estudio mas a fondo de la oferta se presentaron dificultades; se ha intentado conseguir información, pero debido a que es política de estas empresas mantener en reserva los datos, no es posible establecer volúmenes de producción actuales y proyecciones, capacidad instalada y utilizada, planes de ampliación y costos actuales y futuros.

Actualmente la oferta de estos bienes está atendida por un oligopolio con la presencia de pocos productores que copan el mercado.

Con el montaje y puesta en marcha de una planta que produzca toda la gama de Dextrosas y Soluciones electrolíticas y demás derivados, se busca desplazar a los proveedores actuales, lo que equivale a crear

una demanda por sustitución con características de monopolio que son del interés del pais por un solo productor que actúe con carácter oficial y que tenga su sede en el Departamento con los beneficios de generar empleo local, crear valor agregado a la producción departamental y evitar la salida de divisas de la región.

La demanda total debe ser satisfecha por la nueva unidad productora porque se trata de asociar en un solo conjunto a todos los consumidores (hospitales) como socios de la empresa en cuestión constituyendo una Sociedad Limitada.

Es válido el supuesto de una considerable demanda insatisfecha porque los servicios que brindan salud no alcanzan una cobertura ideal, debido a las limitaciones presupuestales con que operan las Instituciones Hospitalarias. Una política tendiente a abaratar los precios de los servicios de salud pueden estimular esa demanda insatisfecha y este proyecto puede contribuir a ese propósito.

Esto se plantea teniendo en cuenta que un porcentaje de habitantes del 40% carece de servicios asistenciales. 2/

2/ MINSALUD. Datos suministrados a la prensa en Marzo de 1977.

1.5. Determinación de Precios

A nivel oficial el gobierno tiene establecido la fijación de precios de productos farmacológicos; el organismo que cumple esta función es el Ministerio de Salud Pública, Oficina de Control de Medicamentos.

Por ser la economía colombiana de corte capitalista, la fijación de los precios también tiene que ver con el juego de la oferta y demanda y naturalmente con el incremento en los costos de materia prima y producción.

Estos elementos juegan un factor importante para que los laboratorios presenten al Ministerio de Salud Pública los análisis y solicitudes para fijación de precios al consumidor.

1.6. Especificaciones de Productos y Uso

La producción como queda dicho se divide en tres grupos así:

1.6.1. Grupo I: Dextrosas y Soluciones

Dextrosa al 5% en A.D. Fco. x 500 cc.

Dextrosa al 5% en tencloruro de sodio 0.45% Fco. x 500 cc.

Dextrosa al 5% en tencloruro de sodio 0.9% Fco. x 500 cc.

Dextrosa al 10% en A.D. Fco. x 500 cc.

Dextrosa al 10% en solución salina Fco. x 500 cc.

Dextrosa al 33% x 250 cc.

Lactato de sodio x 500 cc.

Solución de Hartman x 500 cc.

Solución de Ringer x 500 cc.

Suero fisiológico x 500 cc.

- Modo de Empleo de Productos

Para administración parenteral (intravenosa) con el propósito de mantener o restaurar el equilibrio hidroelectrolítico, ejemplo: en deshidratación por diarreas, por fiebre, por vómito, hidratación por coma diabético, mantenimiento del paciente en cirugía y luego en el posoperatorio, corrección del volumen circulatorio por hemorragia o por choque y otras indicaciones que el médico señale.

Para mantenimiento venoso con el fin de aplicar drogas intravenosas y no causar tantos traumatismos venosos.

También se utiliza para irrigaciones pasando líquidos a través de un cateter a órganos tales como intestino, vejiga, etc.

1.6.2. Grupo II: Bicarbonatos y Electrolítos

Bicarbonato de sodio x 10 cc.

Gluconato de calcio al 10% x 10 cc.

Sulfato de magnesio al 50% x 10 cc.

Cloruro de Potasio al 10% x 10 cc.

Cloruro de Potasio al 31% x 10. cc.

Cloruro de Sodio al 9% x 10 cc.

- Modo de Empleo de Productos

Se utilizan para restaurar el equilibrio electrolítico como complemento de los líquidos parenterales.

Los bicarbonatos de sodio se emplean en acidosis respiratoria o metabólica.

El Cluconato de calcio se emplea en tetánea, deficiencia de calcio y en control del sulfato de magnesio en pacientes eclánticas, pacientes embarazadas con convulsiones e hipertensión.

1.6.3. Grupo III: Agua Estéril

Agua estéril x 1 cc.

Agua estéril x 2 cc.

Agua estéril x 3 cc.

Agua estéril x 5 cc.

- Modo de Empleo de Productos

Su utilización principal es como diluyente de drogas que vienen pulverizadas. Ejemplo: la penicilina, el Allerpen, etc.

1.7. Comercialización, Publicidad, Promoción, Otros

La relación de mercadeo de la unidad productiva con la unidad consumidora se realiza a través de un representante de ventas, a quien los hospitales hacen directamente sus compras.

La distribución y puesta de los productos en manos de los consumidores (hospitales) se realiza por conducto de empresas de transporte, de empresas privadas nacionales o por sistemas de transporte de propiedad de los mismos productores, el costo de transporte por tonelada de Bogotá-Pasto es de $5.000, 3/ que llega a representar hasta un 5% en promedio del costo total del producto. El tiempo entre la formulación del pedido y la recepción de los productos es considerable y oscila entre 30 y 45 dias, y esto amerita que en las Instituciones se provean mecanismos para evitar complicaciones por escasez del producto o productos, y cuando éstas se presentan los hospitales hacen sus compras a intermediarios locales, con agravantes en sus costos y por ende en sus presupuestos.

La comercialización de los productos en lo que hace referencia a las especificaciones del mismo, demuestran que los consumidores prefieren

3/ EL TIEMPO, Mayo 22 de 1983.

la presentación en bolsa plástica por la facilidad en su transporte y manejo.

El crédito que los productores otorgan, está dentro de los términos de comercialización normal 30 y 90 dias.

Por tratarse de productos cuyo uso es eminentemente hospitalario no es necesario un sistema de publicidad y propaganda, a nivel masivo o popular, pero sin descartar que se busca mercado a través de propaganda mediante el obsequio de productores y publicidad con los médicos e Instituciones hospitalarias.

Los costos de comercialización se ven afectados por los gastos de sueldos, viáticos y transportes de los agentes de ventas; así como los costos de transporte de las mercaderías.

El margen de utilidad que las casas productoras dan a los intermediarios en promedio oscila entre un 25% y 30%. En la etapa de comercialización no se considera pérdidas ya que los riesgos están amparados por el mecanismo de seguros de transporte contra toda eventualidad, como ruptura, robo, incendio, etc., esto desde la salida del producto de la factoría hasta la entrega de mercancías al consumidor.

Los canales de comercialización se presentan en un 90% del productor

hacia el consumidor en forma directa, y el 10% restante pasa por la cadena de mayoristas. (Ver Diagrama 1)

La nueva unidad productora para comercialización de los productos empleará los canales directos de productor o consumidor, con lo cual se persigue un oportuno servicio y minimizar costos de comercialización, como publicidad, obsequios, gastos en personal de ventas, márgenes de utilidad a intermediarios y la economía de pago de transporte Bogotá-Pasto.

Es importante destacar que todos estos supuestos se realizan bajo la óptica que esta empresa sea estatal.

1.8. Conclusiones

Es factible el establecimiento de una planta productora de Dextrosas y similares para que abastezca la demanda en el Departamento de Nariño por las siguientes razones:

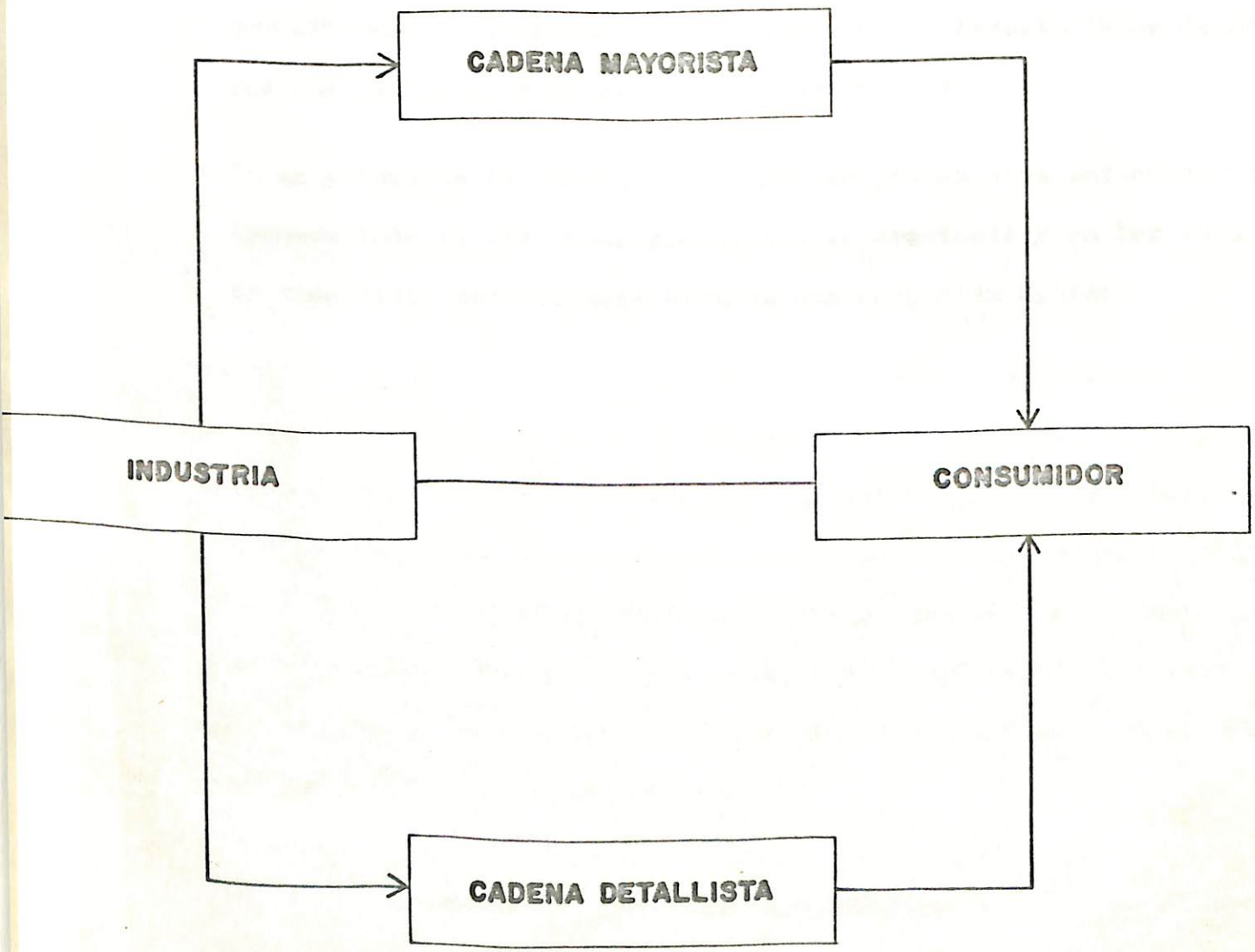
- La principal materia prima que es el agua existe en volumen aceptable de tal manera que garantiza el abastecimiento normal para el funcionamiento de la planta; el resto de materias primas deben ser importadas.

  Se hace la aclaración que por tratarse de una empresa estatal las materias primas no tendrán ningún tipo de gravamen en la importación.

Diagrama.: 1

PLANTA PRODUCTORA DE DEXTROSAS Y ELECTROLITOS

CANALES UTILIZADOS EN LA COMERCIALIZACION



FUENTE: Esta Investigación.

- Existe un mercado para el consumo de la producción total en los hospitales del departamento.

- Con el montaje de esta unidad productora en el departamento se van a obtener beneficios por la eliminación de costos, como es transporte, comercialización y otros.

- La nueva planta entrará como un elemento regulador del mercado estabilizando los precios, permitiendo a las instituciones de salud una utilización de productos a menor costo.

- En un principio la unidad productora se planea para satisfacer la demanda interna del Departamento que va creciendo y en los 10 años de vida útil, del proyecto alcanza una ocupación óptima.

CAPITULO II

DETERMINACION DEL TAMAÑO Y LOCALIZACION DE LA PLANTA

2.1. Tamaño

En la determinación del tamaño se tienen en cuenta los siguientes aspectos:

2.1.1. Capacidad a instalar

En la definición de la capacidad a instalar de la planta en referencia se toma como base la demanda proyectada según Cuadros 5 y 6, y se calcula que se trabajará con una intensidad de ocho horas diarias de Lunes a Viernes, esto con el objeto de minimizar costos de producción y evitar el pago de recargos nocturnos, dominicales, festivos y horas extras. Esta consideración es válida para el despegue de la planta donde su capacidad utilizada será de 58.18% que corresponde a satisfacer la demanda actual, para ir avanzando paulatinamente hasta alcanzar el tope máximo al décimo año de vida útil en un porcentaje del 100% de la capacidad instalada.

Uno de los elementos de decisión que deben tenerse en cuenta para determinar el tamaño de la planta es la cuantía de la demanda que

Cuadro 5

PROYECCION DE LA DEMANDA Y REDUCCION A UNIDAD DE MEDIDA - 1985 - 1994

AÑO	DEXTROSAS		BICARBONATOS		AGUA ESTERIL	TOTAL REDUCCION A 1 cc. PRODUCTO cc.
	FCO. x 500	REDUCCION cc.	FCO.x 10 cc.	REDUCCIONcc.	FCO.x 1 cc.	
1985	303.471	151.735.500	222.051	2.220.510	1.116.975	155.072.985
1986	326.572	163.286.000	275.374	2.753.740	1.234.631	167.274.371
1987	349.673	174.836.500	335.001	3.350.010	1.352.288	179.538.798
1988	372.774	186.387.000	400.932	4.009.320	1.469.945	191.866.265
1989	395.875	197.937.500	473.167	4.731.670	1.587.601	204.056.771
1990	418.976	209.488.000	551.706	5.517.060	1.705.257	216.710.318
1991	442.007	221.003.500	636.549	6.365.490	1.822.914	229.191.904
1992	465.178	232.589.000	727.696	7.276.960	1.940.571	244.806.531
1993	488.279	244.139.500	825.147	8.251.470	2.058.227	254.449.197
1994	511.380	255.690.000	928.902	9.289.020	2.175.883	267.154.903
G R A N T O T A L						2.110.122.037

FUENTE: Esta investigación.

Nota : 5 dias semana x 52 semanas años - 17 dias festivos = 243.

Cuadro 6

TAMAÑO DEL PROYECTO CON BASE EN LA DEMANDA

AÑO	DEMANDA FCO.x 500 cc.	PRODUCCION DIARIA POR CENTIMETRO	PRODUCCION DIARIA POR FCO.500cc.	PORCENTAJE CRECIMIENTO PLANTA
1985	1.276	638.160	1.280	58.18
1986	1.377	688.372	1.380	62.73
1987	1.478	738.843	1.480	67.27
1988	1.579	789.573	1.580	71.82
1989	1.679	839.740	1.680	76.36
1990	1.784	891.812	1.780	80.91
1991	1.886	943.177	1.890	85.91
1992	2.015	1.007.434	2.020	91.82
1993	2.094	1.047.116	2.100	95.45
1994	2.199	1.099.403	2.200	100.00

FUENTE: Esta investigación.

Nota : 5 dias semana x 52 semanas año - 17 dias festivos = 243 dias año.

se va a atender y que en este caso específico se constituye una empresa con características de monopolio, por tratarse de una factoría de propiedad estatal, este planteamiento hace que se elimine la competencia y por lo tanto ofrece un mercado seguro.

Con fines metodológicos se presenta el Cuadro 5 que corresponde a la proyección de la demanda entre los años 1985 y 1994, en el cual todos los productos año por año ha sido reducido a centímetros cúbicos, cuyos resultados se presentan en la última columna. A partir de esta información se obtiene el Cuadro 6 donde se presenta la demanda y la producción en unidades de 500 cc. La producción diaria se obtiene de dividir la producción total reducida a 1 cc. entre 243 dias laborables en el año.

El tamaño de la demanda para el décimo año será de 2.199 frascos por 500 cc. quegn términos de porcentaje significa el 100% de las capacidad instalada, para los años anteriores el porcentaje de utiliza - ción de la factoría se obtiene con base en este dato, y para el primer año con una producción diaria de 1.280 frascos por 500 cc. corresponde a un 58.18%.

2.2. Disponibilidad de Materia Prima y Producción

La materia prima forma parte física de los bienes a producir, de allí

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BIBLIOTECA Y DOCUMENTACION
PROCESOS TECNICOS

que constituye un rubro de gran importancia en este proyecto. La principal materia prima que se utiliza es el agua, la que se emplea en los procesos específicos de producción industrial de los tres grandes grupos: Dextrosas y Soluciones, Bicarbonatos y Agua Estéril.

La localización de la fábrica es importante y debe elegirse el lugar considerando la disponibilidad o fácil acceso al abastecimiento de agua potable, de allí que los sitios preferidos deberán ser el ba - rrio La Carolina o Mijitayo, donde existen acueductos que abastecen la ciudad de este líquido.

Como elementos complementarios a la producción de los medicamentos materia de este proyecto, se utiliza materia prima que deberá importarse y que es la siguiente:

Glucosa
Bicarbonato de Sodio
Gluconato de Calcio
Sulfato de Magnesio
Cloruro de Potasio
Gluconato de Potasio
Cloruro de Sodio
Lactato de Sodio
Solución de Ringer

Los productos anteriores se importarán del Japón y Alemania, el sis-

tema de adquisición a utilizar será recurriendo a licitación con el fin de obtener mejores precios y garantías en la calidad de materias primas para la nueva unidad productora.

Se puede afirmar que esta planta no tendrá dificultades en el abastecimiento de materias primas, por cuanto su volumen primo es de orden natural (el agua) y en cuanto a materia prima importada se hacen los estudios técnicos de consumo que permitan realizar una clara programación especificando cantidad, precios FOB y CIF, tipo de cambio, lugar de origen, forma y duración del transporte, puerto de embarque derechos de aduana, costos y fletes en el pais, comisiones, estimación de posibles mermas, pérdidas de peso y de otra naturaleza no cubiertas por los seguros. Además de las materias primas directas, se utilizarán dentro del proceso de producción, botellas de vidrio para la presentación final del producto, cajas de cartón para el embalaje y distribución al consumidor. Todos los elementos que se acaban de enunciar son producidos en el pais, de allí que pueden obtenerse con facilidad, y a medida que la producción va alcanzando mayores niveles en relación con la planta instalada se va observando que los costos globales de producción disminuyen, presentándose la típica situación de una economía de escala, conservándose en forma constante los costos fijos que en este caso son elevados a lo largo de toda la vida útil del proyecto y considerando que la producción va creciendo en forma moderada año por año.

2.3. Localización

2.3.1. Macrolocalización

La planta estará localizada en el Municipio de Pasto en consideración a los siguientes aspectos:

2.3.1.1. Consumo

En Pasto se halla concentrada la mayor demanda por encontrarse aquí los tres hospitales de mayor capacidad del Departamento, que son: San Pedro, Departamental e Infantil, además la Clínica del Seguro Social que es otro consumidor importante.

El componente de camas hospitalarias instaladas, que es un indicador para oferta y demanda de servicios indica que el 49.15% de la capacidad total del Departamento se encuentra situado en Pasto. En orden de importancia le sigue Ipiales que representa el 10.83%, Tumaco que significa el 9.97%. (Ver Cuadro 7)

Con esta variable soporta aún mas la conveniencia de definir que la planta productora de Dextrosas y similares debe estar ubicada en Pasto.

Cuadro 7

CAPACIDAD CAMAS HOSPITALARIAS INSTALADAS EN EL DEPARTAMENTO 1980

LOCALIDAD	INSTITUCION	No. CAMAS INSTALADAS	PORCENTAJE CAP.INSTITUCION	DIAS CAMA DISPONIBLE	DIAS CAMAS OCUPADAS	PORCENTAJE OCUPACION
Pasto	Departamental	122		46.302	33.257	71.8
Pasto	Infantil	83		30.372	18.712	61.6
Pasto	San Pedro	95		34.702	26.949	77.7
Pasto	Clínica I.S.S.	40		14.600	11.680	80.0
SUB-TOTAL		345	49.15	125.925	90.598	71.95
Sandoná	Clarita Santos	24	3.42	8.893	5.978	67.2
Túquerres	San José	58	8.26	21.257	9.772	46.0
Samaniego	Lorencita V.	27	3.85	9.756	4.554	46.7
La Unión	Eduardo Santos	26	3.70	9.516	7.509	78.9
La Cruz	Buen Samaritano	15	2.14	5.490	3.155	57.5
San Pablo	San Carlos	20	2.85	7.320	4.774	65.2
Ipiales	San Vicente	76	10.83	27.816	19.147	68.8
Tumaco	San Andrés	70	9.96	25.620	19.016	74.2
Barbacoas	San Antonio	30	4.27	10.980	6.206	56.5
El Charco	Sagrado Corazón	11	1.57	4.094	2.068	50.5
T O T A L		702	100.00	256.230	173.677	67.78

FUENTE: Anuario Estadístico 1980, Servisalud Nariño.

Esta Investigación.

Además de lo anterior Pasto se constituye en el paso obligado del tráfico comercial para los municipios de influencia del proyecto, porque se encuentra aquí la sede del Servicio Seccional de Salud de Nariño de la cual dependen administrativa y financieramente los hospitales del Departamento que hacen parte del Sistema Nacional de Salud del pais.

2.3.1.2. Facilidad de Servicios

El Municipio de Pasto, posee servicios públicos como Acueducto y Alcantarillado, Energía Eléctrica urbana y rural, Teléfono local y servicio automático de larga distancia, correo y telégrafo.

Este conjunto de recursos garantizan un funcionamiento adecuado de la nueva planta; además de lo anterior la capital del Departamento posee toda una red de entidades financieras, entre ellas se tiene:

Bancos Comerciales
Bancos de Fomento y Desarrollo
Entidades Agropecuarias
Corporaciones Financieras

2.3.1.3. Población

El Departamento de Nariño cuenta con una población estimada para

1981 de 1'050.489, el 33.38% de esta población está localizada en el Municipio de Pasto, áreas urbanas y rurales (Ver Cuadro 8), como se puede observar aquí se encuentra la mayor concentración de población, facilitándose con esto la consecución de mano de obra calificada como no calificada, para la nueva fábrica, teniendo en cuenta además que la población estudiantil cuenta con dos Universidades, 4 centros de capacitación a nivel técnico superior y numerosos establecimientos de educación media y primaria.

2.3.1.4. Vias de Comunicación

Infraestructura terrestre: la capital del Departamento de Nariño, Pasto se halla comunicada con los demás municipios de la zona de influencia del proyecto a través de carretera.

El Departamento de Nariño posee 3.265 kilómetros de carretera, la extensión por tipo de carretera es la siguiente: 4/

Pavimento	278 kilómetros
Afirmado	1.861 "
Sin afirmar	1.126 "

Las carreteras sin afirmar son utilizadas prácticamente en épocas de verano.

4/ PLANEACION NACIONAL. Estudio Fronterizo Nariño-Putumayo.

Cuadro 8

POBLACION ESTIMADA PARA EL DEPARTAMENTO DE NARIÑO

1981

REGIONAL	SEDE	POBLACION ESTIMADA 1981	PORCENTAJE
Regionales I - II	Pasto	350.609	33.38
Norte	La Unión	126.360	12.03
Centro-Occidental	Túquerres	137.248	13.02
Occidental	Tumaco	218.558	20.81
Sur	Ipiales	175.474	16.70
Area penetración		42.240	4.02
T O T A L		1.050.489	100

FUENTE: Anuario Estadístico - Servisalud Nariño, 1980

La zona Andina es la única región que cuenta con vias pavimentadas en una extensión de 278 kilómetros de los cuales el 70% son de carretera Panamericana y el 30% restante se distribuye en cuatro pequeños ramales así: Pasto El Encano 10 kilómetros, Ipiales Las Lajas 8 kilómetros, Ipiales Túquerres El Pedregal 84 kilómetros, los 176 kilómetros restantes se refieren a la carretera Rumichaca-Rio Mayo.

Los hospitales del Departamento se comunican con la capital por medio de vias carreteables y la distancia respectiva se puede ver en el Cuadro 9 y Mapa 2.

2.3.1.5. Telefonía

La red de microondas de Colombia está interconectada a la ecuatoriana por el enlace de Túquerres-Tulcán. El número de canales en operación en ese sector es el siguiente:

Cali	-	Pasto	180
Pasto	-	Popayán	24
Pasto	-	Quito	36
Cali	-	Quito	36

En Pasto funciona una central de conmutación automática telefónica (ARM-50) para llamadas de larga distancia y otra telegráfica (TW-39).

Cuadro 9

DISTANCIAS ENTRE PASTO Y LOS HOSPITALES DEL DEPARTAMENTO

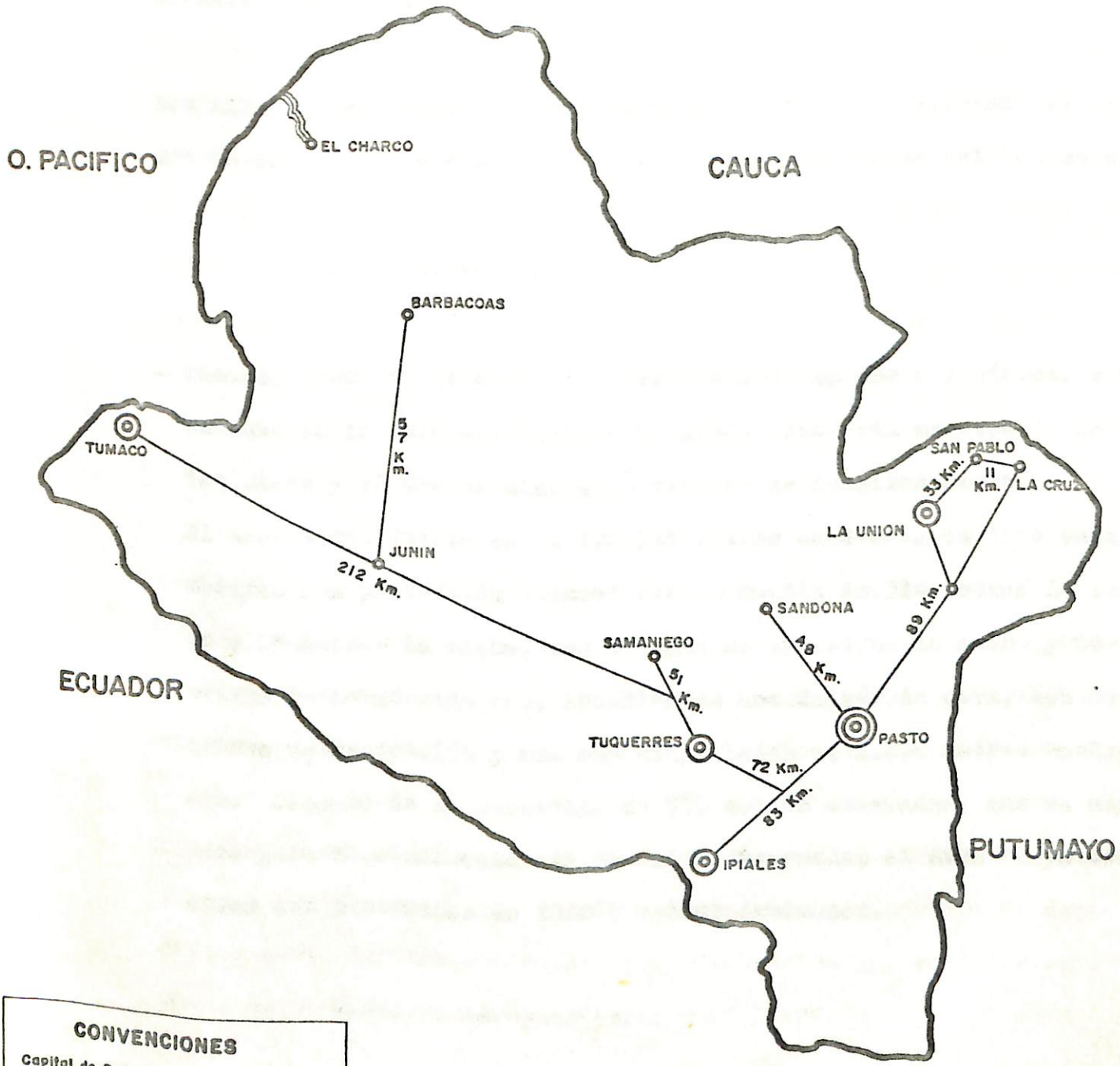
LOCALIDAD	DISTANCIA A PASTO	TIPO CARRETERA
Ipiales	83 Kms	Pavimento
Túquerres	72 "	Pavimento
Samaniego	123 "	Pavim./Afirmada
La Unión	89 "	Afirmada
San Pablo	122 "	Afirmada
La Cruz	100 "	AFirmada
Tumaco	304 "	Pavim./Afirmada
Sandoná	48 "	Afirmada
El Charco	304 (hasta Tumaco)	Afirmada/via fluvial
Barbacoas	236	Pavim./Afirmada

FUENTE: PLANEACION NACIONAL. Estudio Fronterizo Nariño-Putumayo.

MAPA.: 2

DEPARTAMENTO DE NARIÑO

CROQUIS DE RUTAS



FUENTE: MOOP, Policia Vial de Nariño, Esta Investigación.

Esta última tiene 50 abonados télex conectados a la red automática. Los proyectos de telefonía rural están en la fase de diseño de los enlaces y de selección de las localidades.

Los enlaces por líneas físicas se hacen desde 13 localidades de origen de los cuales uno solo pertenece a la Intendencia del Putumayo.

2.3.1.6. Puertos

- Tumaco. Está situado en el extremo sur de la Costa Pacífica, exactamente en la Isla del Morro a un grado cincuenta minutos de latitud norte y 78 grados cincuenta minutos de longitud oeste.
  El tamaño del Puerto es de 122.935 metros cuadrados de tipo rada abierta con protección natural con un muelle de 310 metros de largo y 15 metros de ancho, dos bodegas de 15 metros de ancho y 60 metros de largo cada una, localizadas una detrás de otra, con 20 metros de separación y una capacidad total de 4.000 metros cuadrados. Dispone de un cobertizo de 900 metros cuadrados, que se utiliza para el almacenamiento de madera aserrada, el área de patios ocupa una superficie de 30.000 metros cuadrados.

2.3.1.7. Aeropuertos

Los aeropuertos en la región han suplido las deficientes comunicacio-

nes terrestres y complementan las vias fluviales o marítimas. Pero a medida que las vias terrestres surgen el transporte aéreo se vuelve selectivo. Los problemas de mantenimiento y las interferencias por causas metereológicas, implican que los itinerarios aéreos sufran frecuentes demoras o suspensiones. De ahí que las estadísticas sobre el movimiento de pasajeros y de carga presentan irregularidades en sus tendencias ascendentes. El aeropuerto Antonio Nariño de Pasto tiene una importancia cinco veces mayor que la correspondiente a los aeropuertos de Ipiales y Tumaco. Cabe destacar que Ipiales ha duplicado el movimiento de pasajeros en cinco años.

2.3.2. Microlocalización

Definida la ciudad de Pasto como la localización para la nueva planta, se analiza a continuación el sitio específico donde se producirá el montaje. Para obtener este objetivo se tienen en cuenta las siguientes alternativas: La Carolina, Mijitayo, Pandiaco y Chapal.

Se seleccionaron estos sitios por ser urbanizados y encontrarse en la zona periférica de la ciudad, recomendable por asuntos de desechos y contaminación ambiental, debe destacarse que en todas estas zonas hay abastecimiento de servicios públicos.

Tal como puede deducirse del Cuadro 10, el suministro de agua pota-

Cuadro 10

INFRAESTRUCTURA BASICA DE LOS SECTORES SELECCIONADOS PARA LA MICROLOCALIZACION

SECTOR	AGUA POTABLE *	ESTADO CONSERVACION*	ALCANTARILLADO*	RED ENERGIA ELEC**	COSTO TERRENO*** M2
La Carolina	40L xSeg.	Bueno	Bueno	Suficiente	1.000
Mijitayo	30L xSeg.	Bueno	Bueno	Suficiente	1.500
Pandiaco	-	Regular	Bueno	Suficiente	2.000
Chapal	-	Bueno	Bueno	Suficiente	2.000

FUENTE: * EMPONAR.

** CEDENAR.

*** ICT - Costos/83.

ble, que es la materia prima esencial para el funcionamiento del proyecto ofrece las mejores garantías en el sector de la Carolina, en el resto de sectores el suministro de agua es de un volumen inferior de acuerdo a las informaciones obtenidas directamente en la fuente. En estas inmediaciones está ubicada la planta de agua potable Centenario que es la de mayor capacidad y produce 420 litros por segundo.

En cuanto al estado de conservación de las redes de acueducto se puede afirmar que en general son buenas a excepción de la zona de Pandiaco que está recargada y además son tuberías viejas según concepto de funcionarios técnicos de Emponar.

El sistema de alcantarillado para los cuatro sectores es bueno, ofreciendo las mismas garantías.

El fluido eléctrico puede suministrarse en las mismas condiciones para cualquiera de los sectores considerados, pero es de anotar que en un período de 4 años la ciudad sufrirá un racionamiento de aproximadamente 20% del consumo requerido; información obtenida directamente de Cedenar; con el objeto de remediar esta situación y no tener parálisis en la producción el proyecto requiere que en su plan de inversiones contemple una planta generadora de energía de emergencia.

Los costos de terreno para cada uno de los sectores en cuestión se representan en la columna 5 del Cuadro 10, siendo el mas ventajoso el del sector Carolina con un costo por metro cuadrado de $1.000, este costo se refiere a terreno urbanizado, es decir que tiene infraestructura de acueducto, alcantarillado y energía eléctrica.

2.4. Conclusión

Por todas las consideraciones anotadas, el sitio que mejores garantías ofrece para la instalación de la nueva fábrica, es el sector La Carolina, ubicado en el Municipio de Pasto.

CAPITULO III

INGENIERIA DEL PROYECTO

El propósito que persigue el estudio en esta parte, es ofrecer la imagen completa del funcionamiento interno, indicando las características y generalidades de los productos que van a producirse, las diversas etapas por las cuales atraviesa las materias primas hasta llegar a la obtención de los productos finales.

Se ha considerado que este capítulo constituye una de las partes centrales del estudio, de allí que haya sido preciso prolongar la investigación hasta fuentes de la mas alta confiabilidad como la Farmacopea de los Estados Unidos, según se indica en el Anexo 2.

Las Dextrosas y demás soluciones electrolíticas se aplican en los casos de rehidratación de las personas, en los que se busca aproximar el nivel de electrolitos del paciente al del plasma normal o de soporte de vida mediante el suministro de agua, electrolitos y calorías, en los cuales se mantiene el nivel de plasma normal de paciente. Para que los productos a elaborar puedan garantizar su aspecto clínico de recuperación o soporte de los pacientes, la composición de las soluciones debe ser estandarizada y precisa. La garantía de esterilidad debe ser asegurada en forma terminante por seguridad de los pacientes.

3.1. Etapas Generales. Diseño del Proceso de Producción 5/

En forma general el proceso de producción de dextrosas y similares consiste en tomar una determinada cantidad de agua para inyección, adicionarle las sustancias requeridas de acuerdo con la formulación específica, agitar hasta lograr una mezcla homogénea, filtrar para remoción de las partículas finas no disueltas, envasar y finalmente esterilizar en autoclave. Es una planta Industrial de producción masiva, sin embargo, cada una de estas etapas requiere de equipos técnicamente diseñados, que operen en las mejores condiciones y estén dispuestos en forma suficientemente flexible para que permitan una operación continua de la planta y de unas prácticas de operación y de manejo que impidan contaminaciones fisicoquímicas o bacteriológicas que alteren la calidad deseada del producto. El esquema simplificado del proceso se puede ver en el Diagrama 2.

Identificadas en esta forma cada una de las etapas del proceso de producción se procede a detallar cada una de ellas:

3.1.1. Acondicionamiento del Agua

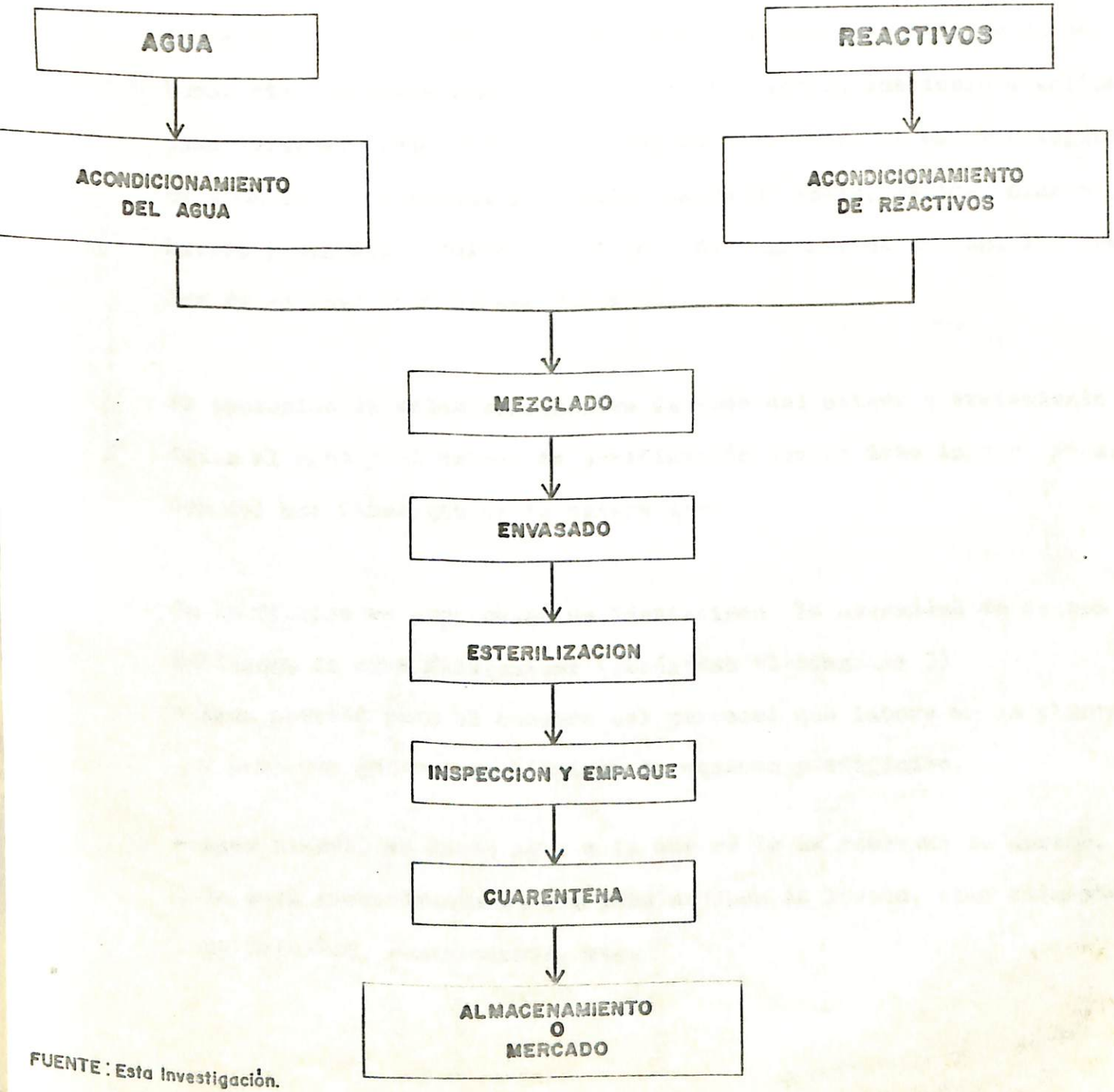
El agua es la sustancia de mayor uso dentro del proceso de producción de soluciones electrolíticas y dextrosas, ya sea como parte constitutiva de ellas o como elemento de limpieza indispensable.

5/ SERVISALUD-Valle. Planta de Parenterales, 1982.

Diagrama.: 2

PLANTA PRODUCTORA DE DEXTROSAS Y ELECTROLITOS

ESQUEMA SIMPLIFICADO DEL PROCESO



FUENTE: Esta investigación.

La principal fuente de agua local está constituida por la red de agua potable que cubre todo el Municipio y dadas las dimensiones de la planta se encuentra conveniente utilizar este suministro.

Los componentes o materiales que acompañan el agua aun en forma potable son: gases disueltos como oxígeno, nitrógeno, dióxido de carbono, etc., materia orgánica, materia suspendida insoluble conocida como turbidez, color como resultado del contenido de materia orgánica y materia suspendida insoluble, sales de sodio, sílice, alúmina, hierro y magneso y sales de calcio y de magnesio disueltas, las cuales se conocen como dureza del agua.

El contenido de estos componentes depende del origen y tratamiento dados al agua y el estado de purificación que se debe lograr, dependen del uso final que se le quiera dar.

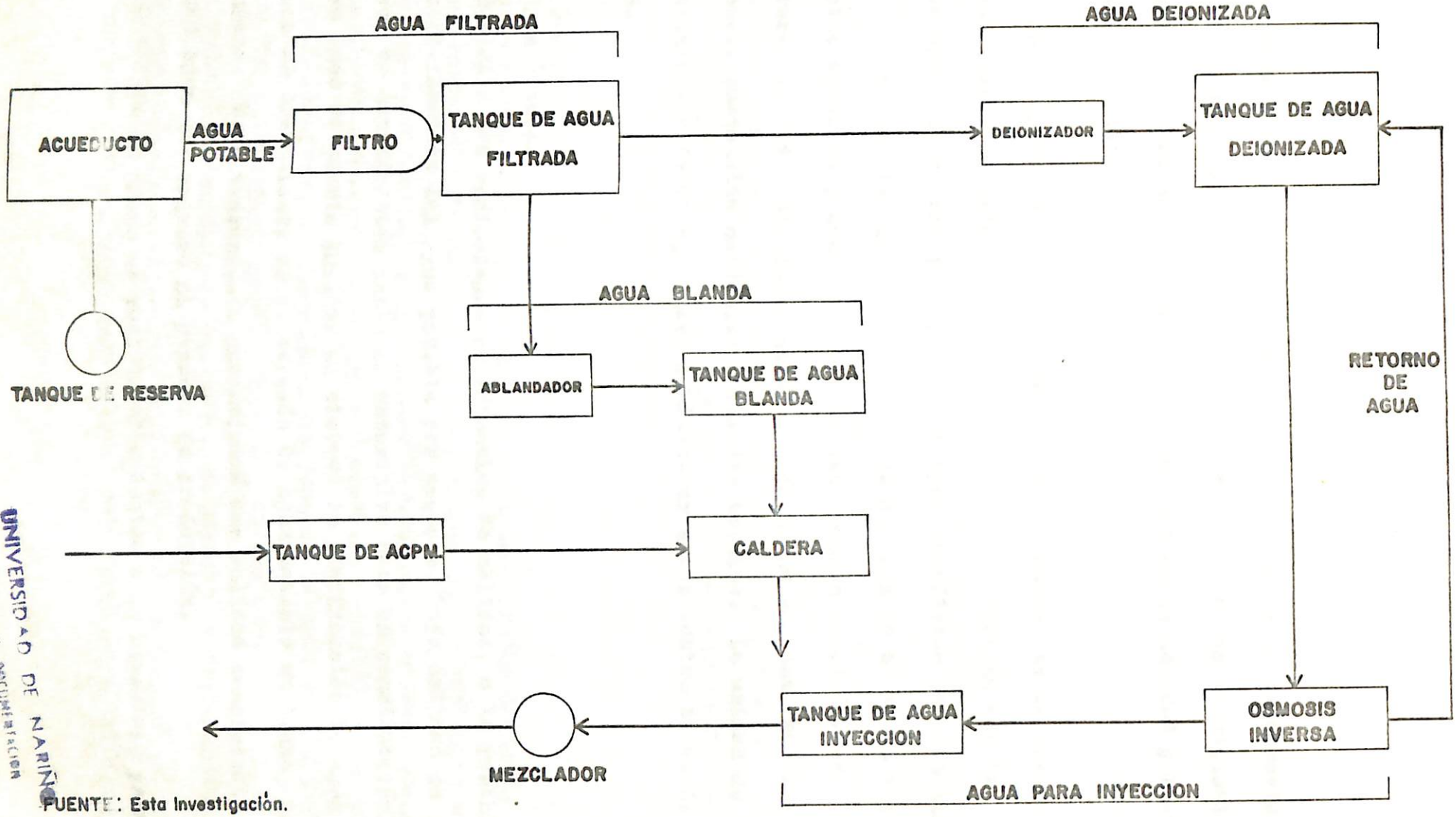
En la fábrica en proyección se identifican la necesidad de cuatro calidades de agua diferentes: (obsérvese el Diagrama 3)

- Agua potable para el consumo del personal que labora en la planta y para uso general en limpieza de equipos y edificios.

- Agua blanda, es decir agua a la que se le ha removido la dureza, la cual generalmente se usa para equipos de lavado, como alimento de calderas, evaporadores, etc.

Diagrama : 3 PLANTA PRODUCTORA DE DEXTROSAS Y ELECTROLITOS
PROCESO DE PRODUCCION. ACONDICIONAMIENTO DE AGUA.

PASTO —— 1.983



FUENTE: Esta Investigación.

UNIVERSIDAD DE NARIÑO

- Agua deionizada, que es agua a la cual no solo se le ha removido la dureza sino el resto de iones, que contenía el agua original. Su uso principal es en laboratorios de control de calidad y lavado de materiales y equipo.

- Agua para inyección, que como su nombre lo indica, es la que se va a hacer parte principal de las soluciones. De acuerdo con la Farmacopea de los Estados Unidos, es agua purificada por destilación o por ósmosis inversa. Esta clase de agua no contiene sustancias aditivas y debe cumplir con las pruebas de pirógenos, PH, cloruro, sulfato, amoníaco, calcio, dióxido de carbono, metales pesados, sustancias oxidables y sólidos totales. La unidad de acondicionamiento de agua debe suministrar estos cuatro tipos de agua.

-- Agua Potable

Debido a las variaciones estacionales de calidad, a la posible contaminación del agua potable por escapes, baja calidad de la red de distribución tanto en materiales como en construcción, se hace necesario iniciar el sistema de purificación de agua con un tratamiento de filtración de agua potable en lecho de arena. Este tratamiento garantizará una calidad consistente del agua que ingrese al proceso de producción.

El filtro de arena es recomendable debido a su capacidad para

remover eficientemente sabores, olores y colores, así como bacterias presentes. Como la cantidad de sólidos disueltos en el agua potable es relativamente baja, se selecciona un filtro de arena rápido como la primera unidad de la planta de acondicionamiento de agua.

Debido a la posibilidad de daños o problemas de suministro de agua potable por parte de la red de abastecimiento y que es necesario asegurar que la planta se mantenga en operación regular, se debe contar con un tanque de agua de proceso necesaria para un día de operación. El tanque debe ser de tipo cerrado y construido en poliester reforzado con fibra de vidrio. Este material debido a su estabilidad y durabilidad es el mas recomendado para este tipo de uso.

-- Agua Blanda

Agua blanda es aquella a la cual se le ha removido la dureza representada por iones de calcio y magnesio. El principal uso del agua blanda en la planta será como alimento a la caldera donde se convertirá en vapor de agua a alta presión con el objeto de ser usado en las autoclaves para la esterilización final de los productos y la esterilización de equipos.

Debido a que en la caldera ocurre un proceso de evaporación, el agua alimentada debe reunir unos requisitos mínimos que aseguren la integridad de tal equipo. Específicamente, el agua

para calderas debe estar exenta de sustancias corrosivas que formen espuma y escala. Las sustancias que forman escala son aquellas que siendo solubles en el agua precipitan en forma de cristales que se adhieren a la pared de la tubería interior de la caldera cuando el agua se calienta, es decir son sustancias cuya solubilidad disminuye con la temperatura. Los depósitos así formados no solo obstruyen el libre paso del flujo de agua, taponando los conductos, sino disminuyen la eficiencia térmica de la caldera, ya que permiten el paso del calor producido en la caldera, hacia el líquido que está evaporando. Las sustancias que deben ser eliminadas son sulfatos, cloruros y carbonatos de calcio y magnesio. El método de ablandamiento mas usado es el llamado intercambio catónico de sodio, durante el cual el sodio reemplaza el calcio y magnesio de las sales mencionadas. La regeneración respectiva se logra con una solución de cloruro de sodio en el cual el sodio se intercambia nuevamente con calcio y magnesio para restaurar la capacidad de resina. Debido a que el agua blanda se utiliza principalmente como alimento a la caldera y que un buen porcentaje del vapor usado en esterilización es recuperable como condensado, es necesario diseñar tanques de almacenamiento adecuados para este fin.

-- Agua Deionizada

Agua deionizada es aquella a la cual se la ha removido un por-

centaje muy cercano al ciento por ciento de todas las especies ionizadas inicialmente presentes. Típicamente, un residuo ionizado total de 3 a 5 partes por millón caracterizan este tipo de agua.

Agua de esta calidad es necesaria en pruebas de laboratorio de alta precisión, en lavado y enjuague de los envases de vidrio y como agua de alimento al equipo de ósmosis inversa. Esta última aplicación se justifica debido a que la calidad del agua producida por el equipo de ósmosis inversa depende de la calidad del agua de alimento.

En esta forma, alimentando agua deionizada de alta calidad a dicho equipo se asegura una óptima calidad del agua para inyección.

El agua deionizada para la planta se produce a partir del agua potable filtrada tomada del tanque de almacenamiento respectivo y haciéndola pasar a través de un equipo deionizador.

Un equipo deionizador es un sistema de dos unidades, generalmente automático que contiene dos lechos o columnas de resina de intercambio iónico. La primera columna se encarga del intercambio catiónico y la segunda del intercambio aniónico.

El uso del agua deionizada en la planta será como alimento para el equipo de ósmosis inversa y agua de lavado de botellas principalmente. El equipo de ósmosis inversa es alimentado con el agua deionizada y produce dos flujos: uno de agua para inyección

y otro de agua rechazada. En este caso el rechazo es agua de excelente calidad por lo que no se considera conveniente desecharla, sino enviarla de nuevo a un acumulador o tanque de agua deionizada. Este tanque se justifica además porque es necesario tener una reserva que permita a la planta seguir operando en el caso de un corte del suministro de agua potable. De este tanque se alimentarán igualmente la lavadora de botellas.
Es conveniente montar dos tanques para evitar contaminación microbiana por un tiempo largo de permanencia del agua en almacenamiento.

-- Agua para Inyección

El agua para inyección, forma parte integral de las soluciones, Por lo que su calidad debe ser estricta, consistente y debidamente controlada.
El proceso de producción de agua para inyección a través de ósmosis inversa consiste en hacer circular a alta presión, generalmente 400 psi o 27.2 atm., agua blanda o deionizada a través de una membrana especial la cual permite solo el paso de agua y retiene en gran proporción las otras partículas contaminadas mencionadas anteriormente. Estos equipos garantizan la eliminación de 90 a 95% de las sustancias orgánicas disueltas, 99% de todas las sustancias orgánicas de peso molecular mayor de 300 incluyendo pirógenos, mas del 99% de las partículas y micro-

organismos y del 90-98% de iones presentes en el agua inicialmente. Obviamente entre mejor sea la calidad del agua de alimento al equipo, menor será la concentración absoluta de impurezas remanentes en el agua para inyección.

Los equipos comerciales de ósmosis inversa no trabajan a eficiencia de producción total sino que parte del agua alimentada se obtiene como producto y parte es rechazada. El agua rechazada se puede recircular al tanque de suministros o usarla para otras operaciones en laplanta. El porcentaje de agua rechazada depende de la calidad del agua alimentada y de la presión de operación del equipo. Los equipos también incluyen un ciclo de lavado automático periódico durante el cual circula agua a alta velocidad removiendo los materiales depositados sobre la membrana.

De acuerdo con los fabricantes de equipos de este tipo, el agua producida es equivalente a agua destilada. Este proceso involucra menos costos de capital y operación, prácticamente no requiere mantenimiento. El consumo de energía así mismo, se estima por lo menos cinco veces menor comparado con el consumo en destilación. Las membranas de ósmosis inversa, según la calidad del agua de alimentación, tienen una vida útil entre 1 y 3 años.

Debido a estas consideraciones, a la garantía que ofrecen los fabricantes de estos equipos de la calidad del agua producida

y a la comprobación de los buenos resultados obtenidos en plantas de soluciones similares que usan estos equipos, se recomienda que el agua para inyección sea producida a través del proceso de ósmosis inversa. Este tipo de equipo debe funcionar continuamente (24 horas al dia) y debido a que es automático no necesitará supervisión constante.

El agua parainyección se usa como elemento básico de las dextrosas, para lavado final antes de llenado de botellas, y para enjuague de equipos en contacto con las soluciones producidas. Debido a que el equipo de ósmosis inversa produce agua para inyección continuamente, mientras la producción de soluciones solo se hará en un turno diurno, se debe contar con un tanque acumulador de agua. Debido a que no es conveniente por el riesgo de proliferación microbiana mantener almacenada agua para inyección mas de 24 horas, se seleccionan dos tanques, cada uno de los cuales puede contener el consumo necesario para 12 horas. De esta forma se asegura bajo tiempo de residencia en cada tanque y el agua no usada durante tal período se retorna al tanque de agua deionizada, después de lo cual el tanque se lava y esteriliza con vapor. Los tanques de almacenamiento de agua para inyección deberán construirse en acero inoxidable.

3.1.2. Acondicionamiento de Reactivos

La etapa de acondicionamiento de materias primas tiene como función principal preparar adecuadamente los reactivos químicos que se emplean en la fabricación de las dextrosas y soluciones.

En el proceso se necesitan tres tipos de reactivos químicos: calidad USP para la elaboración de las soluciones, calidad comercial para uso general y calidad para análisis en el laboratorio de control de calidad.

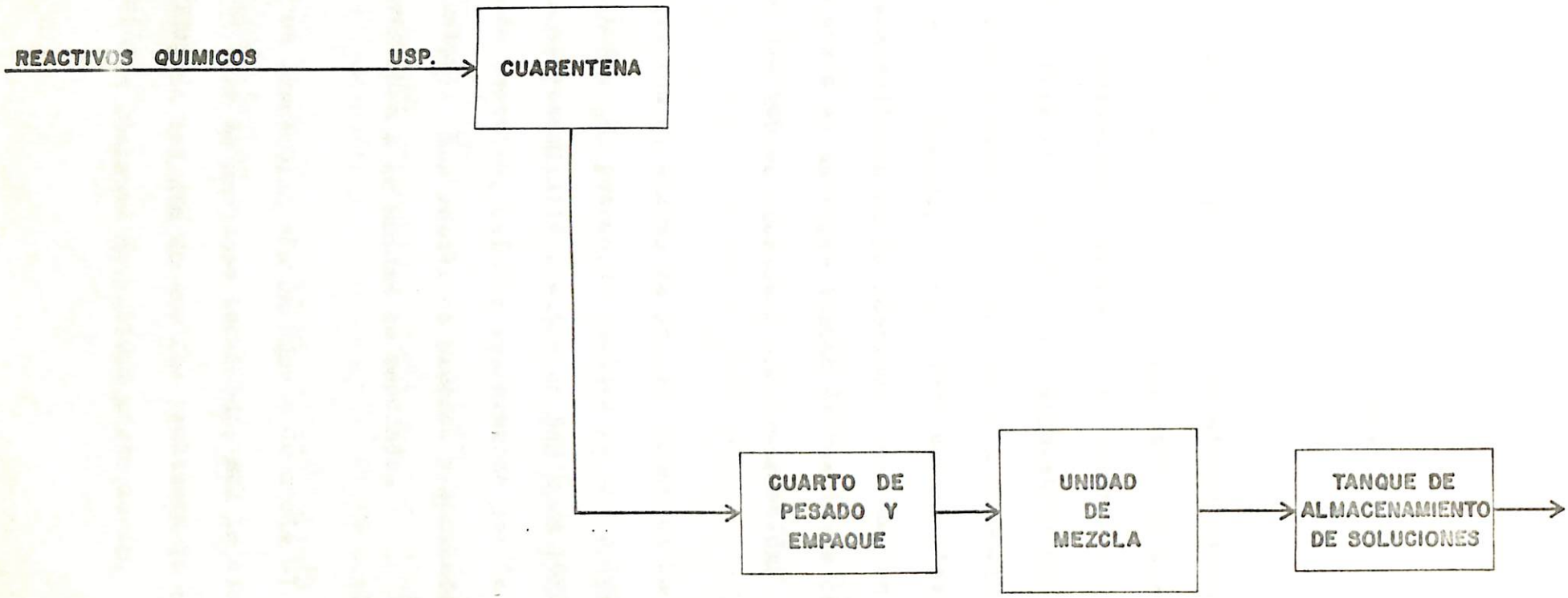
3.1.2.1. Reactivos Químicos Calidad USP

Estos reactivos forman parte de la composición de las dextrosas. Ellos son: dextrosa anhidra, cloruro de sodio, cloruro de potasio, cloruro de calcio y lactato de sodio. Debido al uso tan crítico que ellos tienen, su calidad debe ser en todo momento controlada y su manejo debe hacerse con los mayores cuidados para evitar su contaminación por medios biológicos, físicos o químicos. En esta etapa de acondicionamiento se planean los análisis de control de calidad que se requieren cada vez que los reactivos USP se reciban en el almacén de la fábrica. (ver Diagrama 4)

Durante este tiempo los productos se reservan en cuarentena hasta

Diagrama.: 4 PLANTA PRODUCTORA DE DEXTROSAS Y ELECTROLITOS
PROCESO DE PRODUCCION. ACONDICIONAMIENTO DE REACTIVOS.

PASTO —— 1.983



FUENTE: Esta Investigación.

que hayan cumplido las pruebas de calidad ya establecidas, momento en el cual se autoriza su utilización en el proceso.

En esta etapa también se definen los mecanismos adecuados para suministrar al proceso de mezclado y preparación de las soluciones, las cantidades exactamente pesadas de reactivos USP para cada tanda de preparación. Para este efecto, el responsable de la producción de la fábrica debe elaborar una programación semanal, de acuerdo con las necesidades de despacho, la cual debe ser estrictamente seguida por las diversas unidades de la fábrica. Con base en tal programación, en esta etapa se entregan tandas de reactivos debidamente identificadas cada vez que se proceda a una preparación.

La unidad cuenta con un cuarto de pesado dentro de la zona de bodega de materias primas. El pesado se realiza en una balalza de precisión que asegure la reproducibilidad entre un 95% y un 105% de la cantidad formulada de reactivo, (límite establecido por la farmacopea USP para los productos). Los reactivos pesados y empacados en una bolsa de PVC, se despachan a la unidad de mezclado.

Cada despacho se identifica con un número de serie el cual corresponde al número de lote de producto terminado, con lo cual se facilitará la identificación del dia en que fue realizada la operación para efectos de posibles reclamos de calidad posteriores.

Las materias primas deben someterse en todo caso a las normas de calidad exigidas o establecidas por la Farmacopea USP.

3.1.2.2. Productos Químicos Generales

En esta etapa igualmente se administran y controlan las operaciones en las que se requiere el uso de otros reactivos químicos usados en la fábrica, tales como:

- Supervisar el correcto funcionamiento de los equipos de deionización y ablandamiento y reponer las soluciones de ácido clorhídrico, hidróxido de sodio y cloruro de sodio necesarios para las etapas de regeneración de las resinas de intercambio iónico de tales equipos.
- Continuamente proveer el detergente no iónico necesario para el lavado de las botellas de vidrio en que será envasado el producto.
- De acuerdo con el análisis del agua blanda para la caldera, administrar la cantidad necesaria de reactivos para ajustar el PH del agua al nivel recomendado. Para efectuar estas actividades es necesario contar con un equipo general de laboratorio usado en preparación de soluciones.

3.1.3. Mezcla

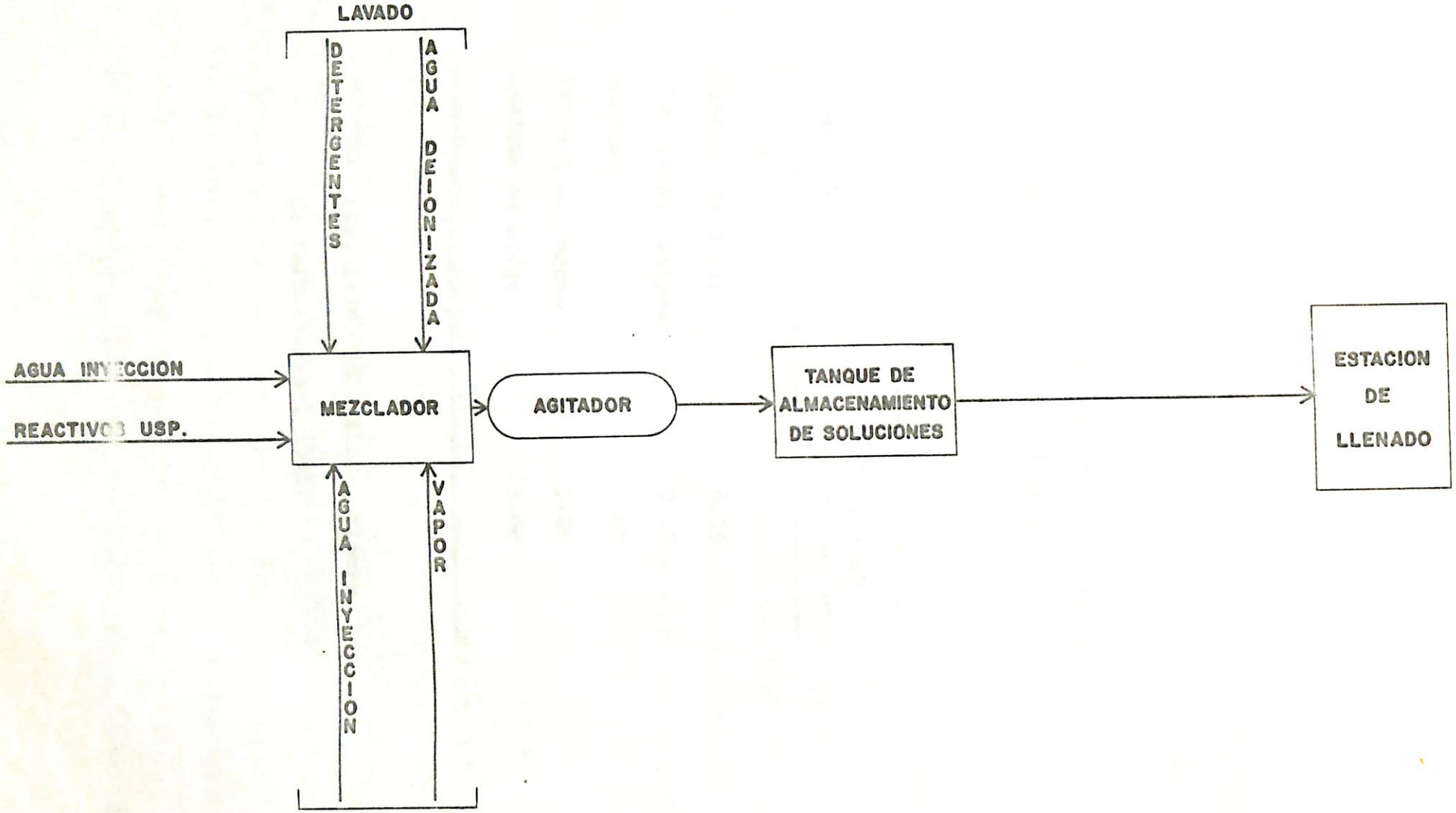
En la etapa de preparación se produce la solución electrolítica según la formulación normalizada. La unidad consta de un recipiente de mezclado al cual se adicionan cantidades precisas de agua para inyección y reactivos químicos calidad USP (ver Diagrama 5). Debido a que la planta producirá diez tipos diferentes de solución, la programación de producción debe hacerse de tal forma que nunca se produzca en un mismo dia de trabajo, mas de un tipo de solución. En esta forma se minimizan no solo las exigencias de lavado del tanque de mezcla antes de producción, sino que se elimina casi absolutamente la posibilidad de que un lote de producción sea etiqueteado erróneamente.

Una vez los reactivos apropiados se introducen al mezclador, se procede a solubilizar y homogenizar completamente los componentes. Para esto, el mezclador debe contar con un agitador de alta velocidad accionada por un motor eléctrico. En el Cuadro 11 se muestran las solubilidades en agua de diversas sales que deben ser mezcladas.
Los datos muestran que todas las sales tienen una muy alta solubilidad en agua lo que aunado a la baja concentración en que ellas se encuentran presentes, facilitan grandemente el proceso de solubilización.

La capacidad del tanque de mezclado se determina de acuerdo con la capacidad de planta estipulada y de ello se hablará en el capítulo de materias primas. El material de construcción debe ser de alta

Diagrama.: 5 PLANTA PRODUCTORA DE DEXTROSAS Y ELECTROLITOS
PROCESO DE PRODUCCION. MEZCLA DE SOLUCIONES.

PASTO —— 1.983



FUENTE: Esta Investigación.

Cuadro 11

PLANTA PRODUCTORA DE DEXTROSAS Y SIMILARES

SOLUBILIDAD EN AGUA A 20°C

COMPUESTO	SOLUBILIDAD Gr. Soluto/ml.agua
Cloruro de Sodio	0.35
Cloruro de Potasio	0.27
Dextrosa	1.00
Cloruro de Calcio	5.00
Lactato de Sodio	5.00

FUENTE: SERVISALUD DEL VALLE. Planta de Parenterales, 1982.

resistencia mecánica a la abrasión, debe poseer una superficie altamente pulida que permita limpieza y esterilización efectivas, no debe desprender ni solubilizar ninguno de los componentes y debe ser químicamente inerte con respecto a los productos con que entre en contacto. El material que cumple tales especificaciones es el acero inoxidable 316.

Con el objeto de facilitar la operación de mezcla y drenaje, el tanque será de forma cilíndrica, fondo cóncavo y poseer además bafles o barreras verticales simétricamente dispuestas alrededor de la circunferencia, que aumentan la eficiencia de mezclado evitando movimientos rotacionales y remolinos, creando en cambio turbulencias. El diseño óptimo de tales bafles recomienda que su ancho sea 1/12 del diámetro del mezclador y que su altura sea un poco menor de la altura que el líquido estático alcance en el recipiente.

Al igual que el mezclador y el agitador, los bafles deben ser construidos de acero inoxidable 316.

Con el fin de facilitar una operación apropiada del mezclador se debe proceder a enjuagarlo con agua para inyección después de que cada tanda de producto haya sido preparada. Esto asegura condiciones asépticas y remoción de cualquier material remanente en el tanque. Al iniciar y al finalizar la jornada, el mezclador debe ser sometido

a una limpieza exhaustiva con detergentes, seguida por enjuagues con agua deionizada y finalmente con agua para inyección. Inmediatamente después se procede a esterilizar con vapor.

Una vez la mezcla ha sido homogenizada se drena por gravedad hacia los tanques de almacenamiento de soluciones, desde donde posteriormente se enviará a la estación de llenado.

Debido a la velocidad de producción de las soluciones electrolíticas que es mayor que la velocidad de envasado se hace indispensable el almacenamiento intermedio de soluciones. Con el fin de minimizar la contaminación en este punto, cada tanque antes de ser utilizado es lavado, enjuagado con agua para inyección y esterilizado con vapor de agua. Los tanques deben ser de acero inoxidable 316 con tapa de sellado hermético y poseer un orificio de desfogue en el cual se instale un filtro de 0.22 micrones para filtración a esterilidad del aire que pueda penetrar al tanque. La capacidad de cada tanque de almacenamiento es exactamente igual al volumen de solución producido en cada tanda del mezclador. Se estima que la solución allí almacenada no va a tener un tiempo de espera mayor de dos horas.

3.1.4. Envasado

Una vez la solución ha sido preparada y almacenada, la siguiente

etapa dentro del proceso es la de envasado.

Debido a que la solución ha sido formada por adición de sólidos se debe realizar una operación de microfiltrado antes de envasar, para asegurar la remoción de materiales insolubles hasta un tamaño de pocos micrones de la solución. Generalmente se aprovecha esta operación de microfiltración para esterilizar simultáneamente la solución a su paso por filtros de 0.22 micrones de diámetro de poro. Este tipo de esterilización es ampliamente utilizado en la fabricación de productos sensibles al calor que no pueden normalmente ser esterilizados con vapor. En este proyecto se recomienda usar microfiltración como una esterilización preliminar por lo que su ubicación se hace en la línea entre el tanque de almacenamiento de soluciones y la máquina envasadora.

Generalmente, el sistema de microfiltración estéril consiste de un prefiltro y un filtro de materiales especializados porosos, cuyo diámetro de poro no solo es uniforme sino muy pequeño. Para filtración estéril se recomienda un diámetro de 0.22 micrones.

El prefiltro está constituido por un material fibroso, granular o sintetizado comprimido, articulado formando una masa con muchos canales de flujo irregulares. Las partículas suspendidas en el fluido que pase a través de esta masa serán retenidas por un mecanismo de absorción y atrapado. Debido a su estructura, no es posible asignar

a este tipo de filtro un diámetro de partícula máxima que permita pasar con la solución.

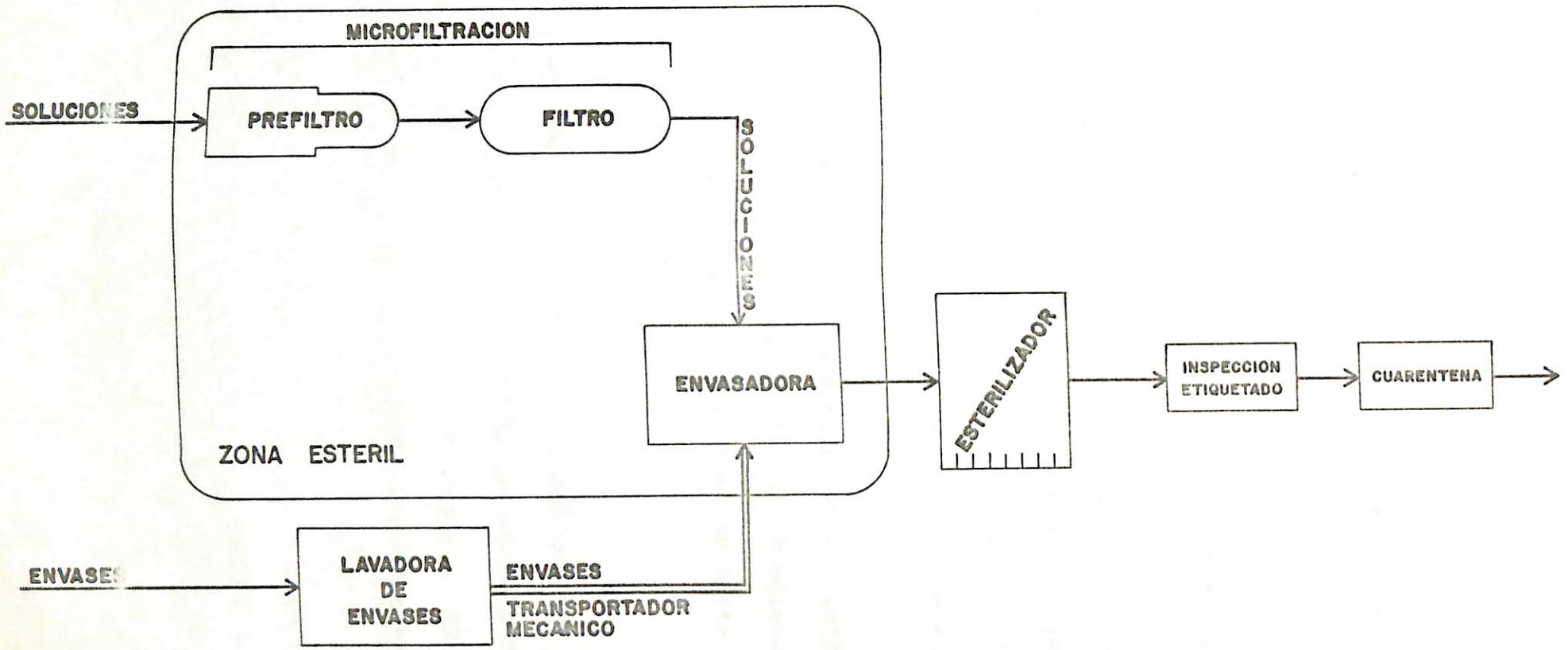
Puesto que este filtro puede colectar contaminantes a través de toda su estructura, su capacidad de remoción de sólidos es alta. Las principales desventajas que tiene se relacionan con la migración de la estructura contaminando el agua, crecimiento de microorganismos especialmente durante largos períodos de trabajo y la imposibilidad de garantizar un tamaño de partícula máxima remanente en solución. Por tal razón materiales de este tipo se usan solo en prefiltros. (ver Diagrama 6)

Una vez la solución ha sido prefiltrada se envía a través de un filtro de membranas el cual es de un material altamente uniforme, de estructura rígida y continua, con orificios uniformemente espaciados que retienen por tamizado partículas de diámetro mayor al del poro; tienen sin embargo baja capacidad de acumulación.

El sistema óptimo de filtración estéril es aquel que combina un prefiltro y un filtro de tamaño y capacidad apropiados, de tal forma que la obstrucción inevitable de los poros del uno o del otro se presente después de que se ha logrado filtrar una cantidad apreciable de solución. Una ventaja adicional que puede ser de gran utilidad para facilitar la operación de filtración estéril es el hecho de que

Diagrama.: 6 PLANTA PRODUCTORA DE DEXTROSAS Y ELECTROLITOS PROCESO DE PRODUCCION., ENVASADO Y ESTERILIZACION DE - PRODUCTOS.

PASTO —— 1.983



FUENTE: Esta Investigacion.

tanto el prefiltro y el filtro puedan ser esterilizados con vapor de agua en el mismo sitio de operación, evitando desconecciones y esterilizaciones en autoclaves independientes las cuales generalmente demanda mucho tiempo y presentan dificultades de manejo.

Este conjunto filtro-prefiltro resiste hasta una diferencia de presión máxima de 3.5 Kg/cm2 a 23°C y 0.35 Kg/cm2, a 127°C durante esterilización con vapor en línea. Su poder de retención microbial se reporta como retención de seudomonas diminutas a un nivel de 10^{10}.

Una vez el producto ha sido filtrado se procede a envasarlo para posteriormente recibir la esterilización final. Tradicionalmente, las soluciones han sido suministradas al público en botellas de vidrio y bolsas o botellas plásticas.

El envase a usar debe ser transparente, prácticamente sin color, autolavable una vez esté lleno, no tóxico, no impartir olores inapropiados a los productos, ofrecer una alta barrera a la transmisión de vapor de agua y no debe contener residuos de partículas sueltas.

En cuanto a botellas de vidrio, la Farmacopea Americana USP XX establece que las soluciones electrolíticas deben ser envasadas en recipientes tipo I (vidrio de borosilicato altamente resistente) o tipo II (vidrio tratado con cal soda).

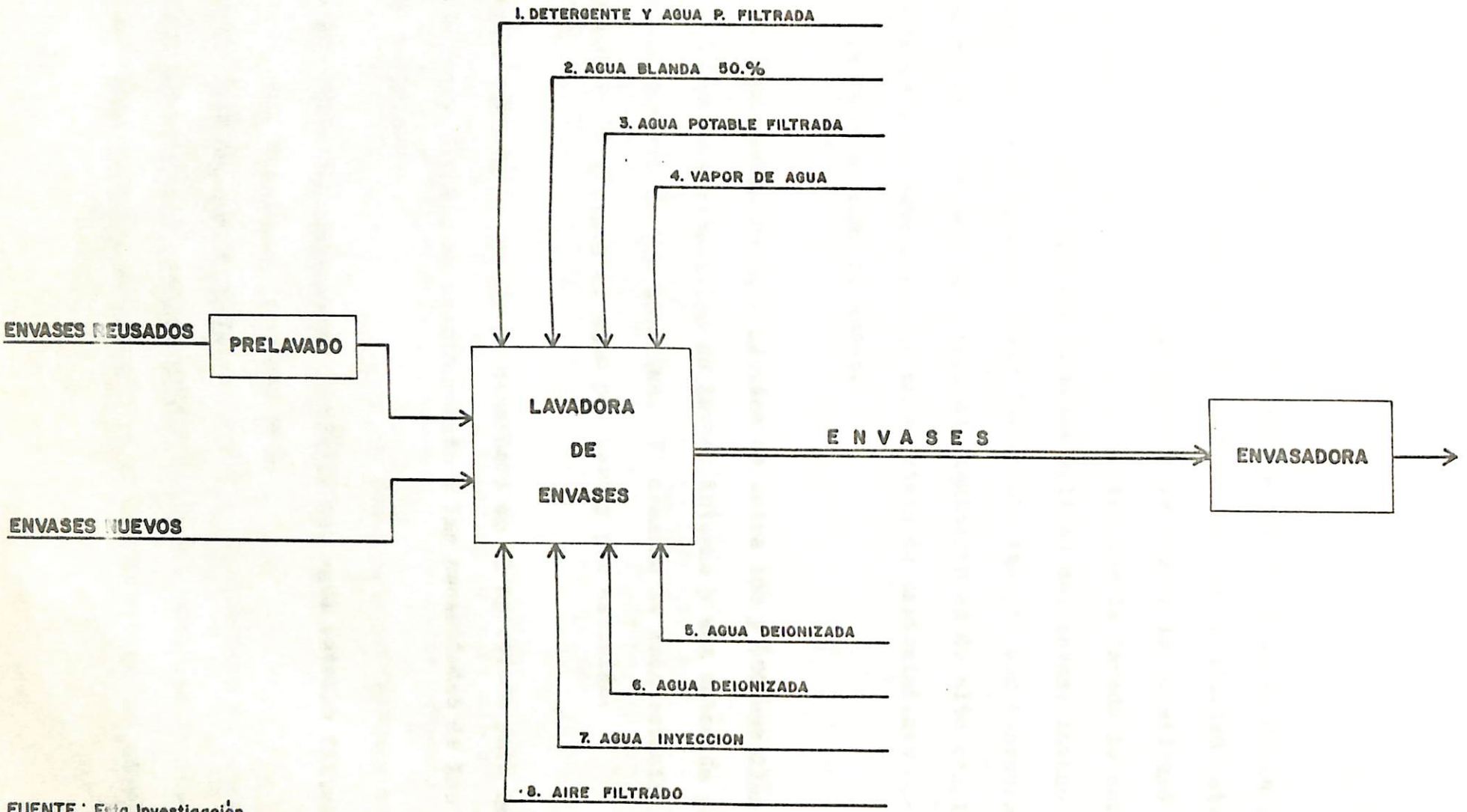
En el mercado nacional se ofrece un envase de vidrio producido por Peldar, el cual está siendo usado para envasar soluciones electrolíticas en algunos laboratorios. También se pueden adquirir frascos de excelente calidad y mayor costo por importación directa de los mismos.

En la nueva fábrica se recibirán tanto botellas nuevas como retornadas desde los diversos centros asistenciales del Departamento, sobre los cuales se debe establecer algún tipo de control que impida que se reutilicen mas de dos veces. El proceso de acondicionamiento de las botellas reusadas empieza con la inmersión de cada botellas en una solución de soda caustica con el objeto de remover cualquier etiqueta de papel que se encuentre aun adherida.

Botellas nuevas y usadas se someten luego a un lavado exhaustivo en un equipo apropiado. La maquinaria mas usada en esta operación es del tipo de movimiento continuo, generalmente rotatorias, las cuales suministran varias estaciones de lavado interno y externo de cada botella que circule.en ella. (Ver Diagrama 7) Todas las partes de contacto con el líquido están fabricadas con materiales resistentes a la corrosión. Durante la operación de estas máquinas el operador únicamente tiene que colocar la botella para ser lavada en forma invertida sobre una aguja y remover una que ya ha sido lavada. La operación de lavado propiamente dicha es totalmente automática.

Diagrama. : 7 PLANTA PRODUCTORA DE DEXTROSAS Y ELECTROLITOS
PROCESO DE LAVADO DE ENVASES.

PASTO —— 1.983



FUENTE : Esta Investigación.

Para determinar la capacidad de la máquina que se necesita en la planta se tomó como base la producción inicial deseada de 310.040 botellas de 500 cc. al año. Otro criterio de selección lo constituyó el que la máquina tuviera un mínimo de estaciones de lavado lo suficientemente alto para asegurar la buena calidad del envase lavado.

Por último, se trató de considerar únicamente equipos con representantes en el pais, ya que este tipo de maquinaria es de alta complejidad mecánica y se debe asegurar un servicio de mantenimiento confiable y oportuno en caso de daños.

La capacidad de lavado de esta máquina es entre 180 y 600 botellas por hora, posee ocho estaciones de lavado interno y una estación para el lavado externo de las botellas. El consumo de cada estación es del orden de 20 galones de agua por hora y por estación.

El siguiente esquema de lavado se considera es el apropiado para mejores resultados finales en consideración a las necesidades de los productos a elaborar:

Estación 1: Emplea un detergente no iónico con agua potable filtrada proveniente de estación 2.

Estación 2: Agua potable filtrada

Estación 3: Agua blanda caliente 50ºC.

Estación 4: Vapor de agua filtrado

Estación 5: Agua deionizada

Estación 6: Agua para inyección

Estación 7: Aire filtrado estéril

FUENTE: Servicio de Salud del Valle. Planta para parenterales, 1982.

La estación de lavado externo se hará con agua potable filtrada. Esta distribución de las estaciones debe ser sometida a chequeo de efectividad en asepsia, tan pronto la producción se inicie. Dependiendo de tal evaluación se sugerirán los cambios internos apropiados.

Debido al alto consumo de agua de diversa calidad que tiene este tipo, se ha decidido recircular el tanque de agua filtrada, el agua proveniente de las estaciones 3, 4, 5, 6 y 7. (Ver Diagrama 7)

Aunque esta agua debe ser de nuevo purificada en la forma discutida anteriormente, la recirculación significa una apreciable economía en el consumo de la fábrica. El agua con detergente proveniente de las estaciones 1 y 2 se desecha de la fábrica.

Simultáneamente, se debe proceder al lavado de los tapones de caucho necesarios para cerrar las botellas. La forma mas efectiva de limpieza es a través de lavado mecánico con un detergente en una máquina

lavadora convencional usando agua caliente, seguido de varios enjuagues con agua deionizada.

Finalmente los tapones se esterilizan en autoclave y se depositan en vasijas adecuadas, antes de ingresar a la zona de envasado de las soluciones. Las soluciones estériles han de ser introducidas en las botellas limpias asegurando continua esterilidad. Para este fin, la operación de envasado debe hacerse en una forma esterilizada tal que prevenga la contaminación microbiana durante el manejo de los materiales. Las principales fuentes de contaminación son el aire y el agua en el área y el personal, materiales y equipos que participan en el proceso. Un salón estéril debe adecuarse para este fin. Esta zona esteril debe tener sus paredes, pisos y techos recubiertos con materiales no porosos de fácil limpieza; debe estar libre de proyecciones arquitectónicas innecesarias, mantener una diferencial de presión positiva para prevenir entrada de aire sin purificar y poseer un sistema de intercomunicación efectivo y que minimice el tráfico de personas y materiales.

Generalmente un área estéril de barrera parcial, como la necesaria para el proceso de llenado, se forma en un espacio cerrado con flujo laminar de aire filtrado a través de filtros de alta eficiencia en la retención de partículas.

El personal, materiales y equipos que entran a la zona estéril constituyen la mayor fuente de contaminación. Por tal razón todas las personas que laboran en dicha área deben seguir estrictas normas de aseo que incluyen el uso continuo de máscaras, guantes, gorro y ropa especial. En el Plano 1 se presenta un detalle de la distribución del área estéril y de los equipos y espacios que la conforman.

El área estéril debe ser celosamente aseada. La limpieza y mantenimiento debe hacerse después de terminar cada dia de trabajo de tal forma que el salón permanezca vacío por algún tiempo antes de empezar la siguiente operación. Se deben emplear así mismo lámparas de radiación ultravioletas especialmente en áreas de acceso y de servicio al personal.

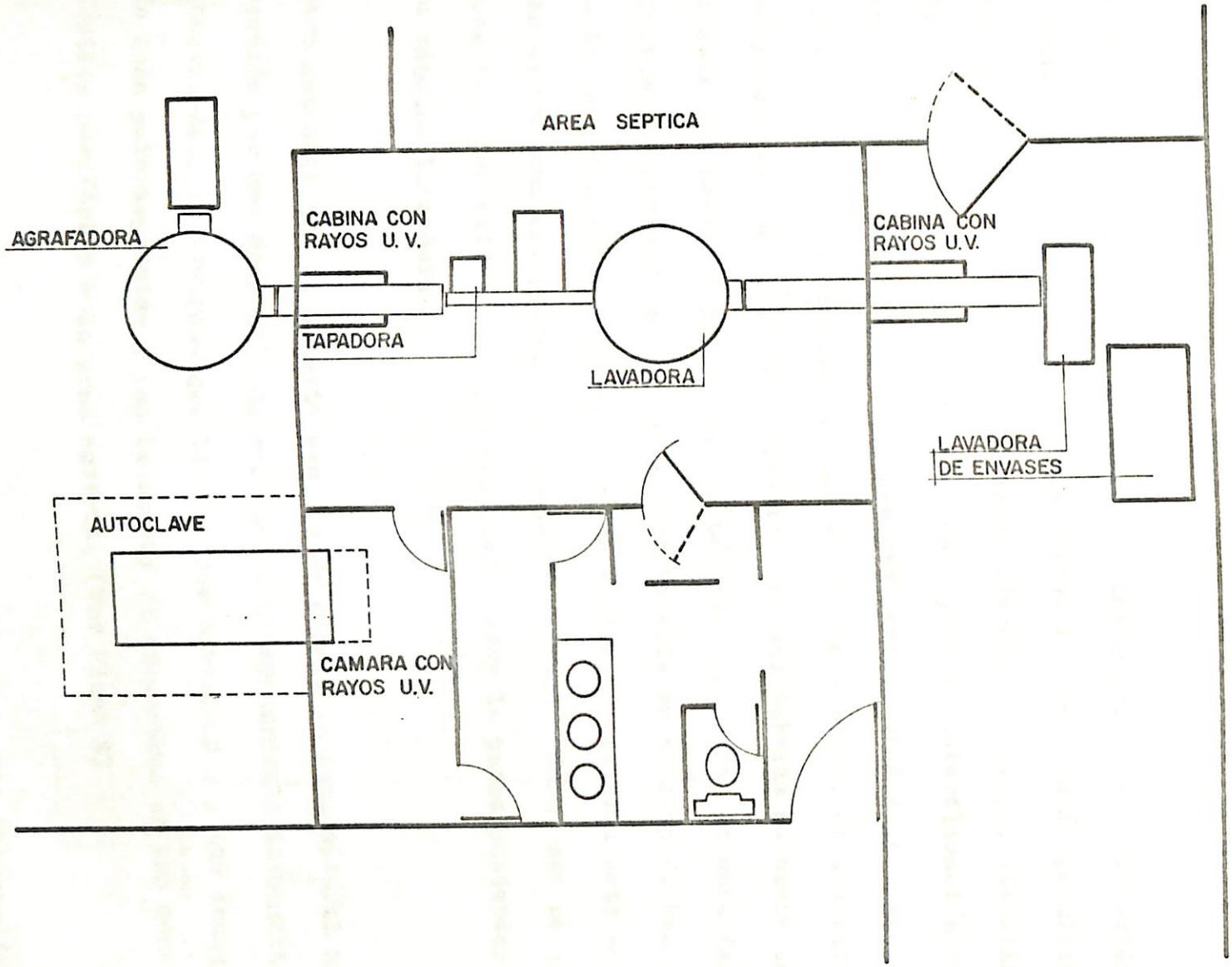
Así mismo, es absolutamente importante validar la efectividad de los cuidados que se tienen para mantener la esterilidad de la zona, tomando muestras periódicas del medio ambiente y haciendo conteo e identificación de colonias desarrolladas en un medio adecuado. En la farmacopea USP XX se describen detalladamente los procedimientos para determinación de esterilidad.

Para la nueva fábrica se recomienda que el envasado se haga en una zona estéril a la cual ingresan por un transportador mecánico a través de un túnel con radiación ultravioleta las botellas que salen de

Plano : 1

PLANTA PRODUCTORA DE DEXTROSAS Y ELECTROLITOS
DISTRIBUCION AREA ESTERIL.

PASTO —— 1.983



FUENTE : Esta Investigación.

la lavadora. Los tapones de caucho se introducen a la zona estéril a través de una autoclave de doble puerta la cual además permitirá introducir a la zona materiales esterilizados como ropa, utensilios, etc. Tal autoclave se usará igualmente para la esterilización del producto terminado. Las soluciones para ser envasadas se bombearán desde el tanque de almacenamiento respectivo a través de los filtros que se encuentran en la zona estéril, por una tubería de acero inoxidable 316 hasta el pistón de una máquina llenadora, la cual debe dispensar volúmenes de 500 cc. a cada botella en el caso de las soluciones y dextrosas. Idealmente, la filtración estéril debe estar tan cerca como sea posible del punto de llenado. Como esto es impráctico, los filtros estarán colocados sobre la pared posterior de la máquina llenadora.

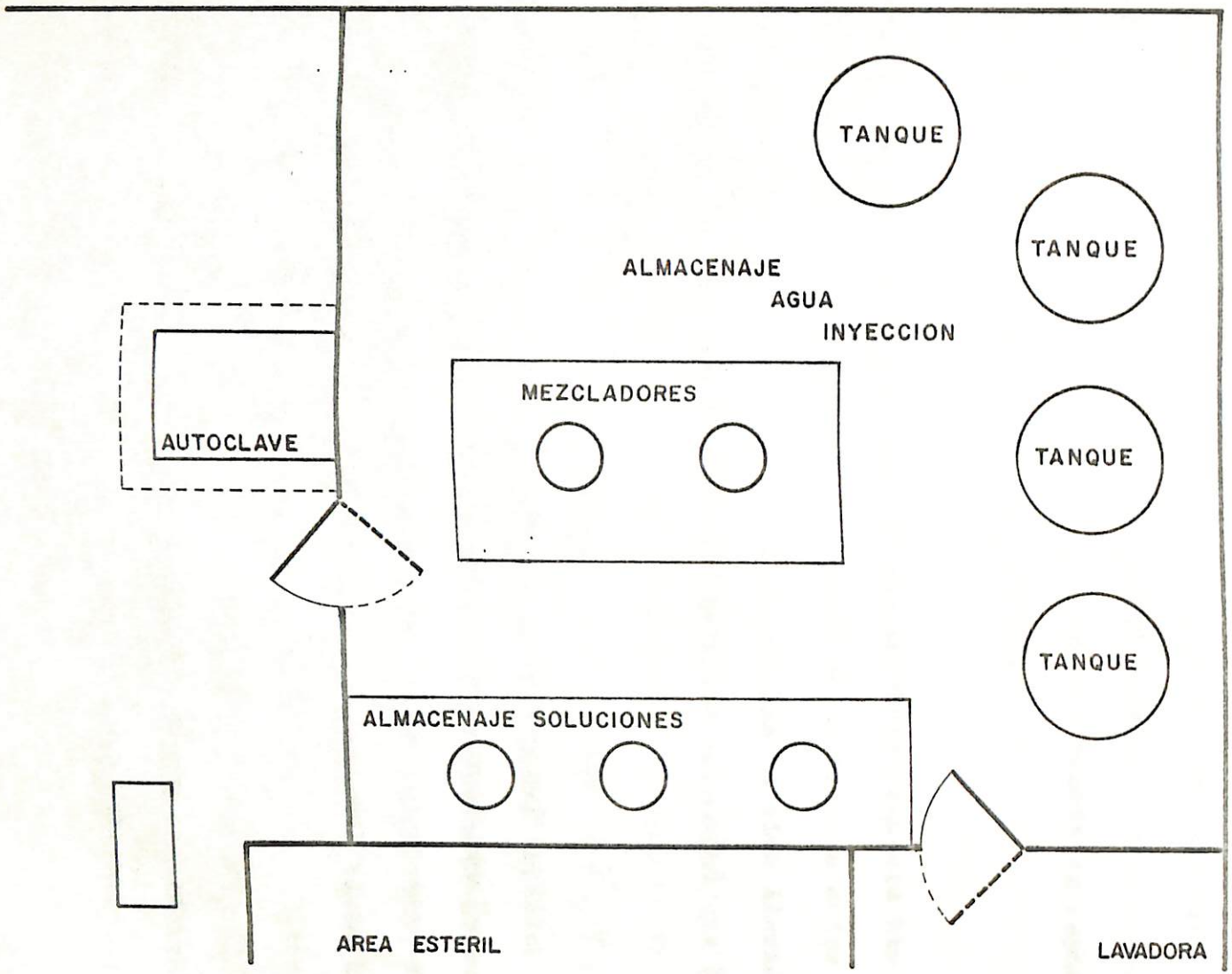
Para asegurar que el cuidado con que se maneja la zona estéril no sea perdido por una operación de mezclado o almacenamiento intermedio inadecuados, se programa que los equipos mencionados y los tanques de agua para inyección y las lavadoras se encuentren en una zona aséptica periférica a la zona estéril. (Ver Plano 2)

Una zona aséptica es aquella que a pesar de no poseer filtración a esterilidad del aire que se impulsa para crear presión positiva, posee control de temperatura ambiente y es cuidadosamente desinfectada con agentes adecuados tales como soluciones de fenol al 1 o 2%, solu

Plano : 2

PLANTA PRODUCTORA DE DEXTROSAS Y ELECTROLITOS
DISTRIBUCION AREA SEPTICA.

PASTO —— 1.983



FUENTE : Esta investigación.

ción de alcohol etílico al 70%, solución de hipoclorito, etc. Para este proceso se recomienda ubicar en el área aséptica las operaciones de lavado de envases, de preparación y mezcla de soluciones de esterilización y los espacios de acceso y cambio de ropas para el personal que labora en el área estéril.

De acuerdo con las necesidades de envasados se requiere una máquina de funcionamiento automático con capacidad de llenado entre 180 y 600 recipientes por hora. Una vez la botella ha sido llenada, es inmediatamente tapada por una máquina de igual capacidad que la máquina envasadora.

Las botellas tapadas continúan en el transportador mecánico hasta salir de la zona estéril a través de un túnel provisto de radiación ultravioleta, una mesa acumuladora desde donde manualmente se las coloca en la máquina agrafadora de aluminio, la cual tiene una capacidad máxima de 600 botellas por hora.

Una vez las botellas están correctamente selladas, se colocan sobre unas canastillas y sobre un carro transportador, el cual las conducirá al proceso de esterilización final.

3.1.5 Esterilización

Con el objeto de asegurar completamente la calidad apirógena y estéril de la solución preparada, se la somete a un proceso adicional de esterilización. Este proceso se lleva a cabo ordinariamente en una autoclave y emplea vapor saturado a presión, (mínimo 8 minutos a 121°C para producir una probabilidad de supervivencia de microorganismos menor de 1 x 60^{-6}).

La temperatura a la cual el autoclave opera es usualmente 121°C medidos por un mecanismo sensor en la línea de descarga de vapor del autoclave. Debido a que el proceso depende tanto de la presencia de humedad como de elevada temperatura, se deben tomar medidas adecuadas que aseguren que el aire se remueva de la cámara antes de iniciar el ciclo de esterilización. El tiempo de exposición del producto (calentamiento, etapa isotérmica y enfriamiento) varía con la naturaleza del producto y el tamaño de los recipientes a ser tratados. Una botella vidrio gruesa de 1.000 ml. puede tomar alrededor de 20 minutos o mas para lograr la temperatura de 121°C; después de que esta temperatura se ha registrado en la línea de descarga.

En caso de esterilización de recipientes rígidos, se pueden desarrollar durante el período de enfriamiento altas presiones internas que pueden ser peligrosas para el operador del esterilizado como resulta-

do de recipientes que estallen. Los recipientes deben tener salidas de ventilación o la autoclave debe tener un sistema de enfriamiento tal que permita remover los recipientes herméticos seguramente.

El uso de un termómetro registrador en la línea de descarga es deseable para propósitos de operación ya que suministra un record permanente de cada ciclo de esterilización.

Es importante chequear la distribución de calor particularmente en autoclave nueva o después de cambios en las condiciones de carga, colocando mecanismos apropiados de registro de temperatura logradas en diferentes planos horizontales y verticales de equipo. Se sugiere que estos mecanismos se inserten en recipientes representativos del producto. Estos mecanismos deben ser capaces de indicar no solo el logro de la temperatura de esterilización sino la duración, y si es necesario, de los tiempos de precalentamiento y enfriamiento.

Las termocuplas o termómetros de registro deben ser periódicamente recalibrados contra termómetros de mercurio certificados.

Con el objeto de asegurar un funcionamiento de la nueva fábrica que no esté sujeto a la posibilidad de daños en equipos tan importantes se recomienda un adecuado mantenimiento preventivo.

3.1.6. Inspección y Empaque

Una vez el proceso de esterilización se ha completado, las botellas se descargan de las canastillas. Se las inspeccionará una a una para comprobar que la botella, tapa y agrafe están en buenas condiciones y que la solución es cristalina. Cada botella es etiquetada en forma semiautomática por una máquina a la que se le han suministrado previamente las etiquetas. Cada etiqueta debe claramente estipular el tipo de solución, la cantidad, el número del lote y la fecha de expiración, la cual es de 2 años después de la fecha de fabricación. La etiqueta debe contener además el nombre de la empresa productora y la composición de la solución.

Cuando la botella ha sido etiquetada se empaca en cajas de cartón que pueden contener 25 botellas. A cada caja se le pone un sello en el que se especifica el nombre del producto y el número del lote, a mas de una tarjeta que especifica que tal lote debe pasar a bodega en cuarentena hasta que Control de Calidad certifique que llena los requerimientos impuestos por la Farmacopea USP.

Una vez el producto ha sido aprobado, puede ser despachado a los sitios de consumo de acuerdo con la programación de ventas.

La planta contará con un laboratorio de control de calidad, el cual

no solo es el encargado de hacer ensayos de calidad a los productos sino a las materias primas que ingresan a la planta. Las pruebas a las que debe ser sometido cada uno de estos elementos serán mencionadas en la parte sobre definición y formulación normalizada de los productos.

La única prueba de control de calidad que se recomienda sea desarrollada por un procedimiento diferente al especificado en la Farmacopea es la prueba de pirógenos.

En lugar de esa prueba se recomienda usar la prueba para endotoxinas de bacterias, la cual se basa en pruebas bioquímicas con el lisado de amebocito del Limulas Polyphemus. Esta prueba está siendo promovida comercialmente por importantes compañías de carácter farmacológico como Báxter-Travenol y Mallinchrodt.

El muestreo estadístico de botellas para hacer el control de calidad se tomará de acuerdo con lo establecido en la Farmacopea, definiendo como lote de producto las botellas que hayan sufrido el proceso de esterilización simultáneamente.

3.2. Distribución de la Planta

Como parte integrante de este estudio se define los ordenamientos

físicos de los equipos de la planta, sus elementos básicos y sus servicios auxiliares, dentro de un espacio que reuna las características establecidas en cada uno de los procesos de producción.

Una de tales características, es que el equipo debe tener una disposición adecuada y una área suficiente para acomodar, en forma funcional y segura todas las instalaciones de la planta.

Para la asignación de áreas se tiene en cuenta cada una de las unidades de planta. Sobre ella se ha hecho la consideración de espacios para procesamiento, mantenimiento de equipo, almacenamiento de materiales, suministro de servicios, ubicación de operarios, considerando la expansión de la planta con el transcurso del tiempo.

3.2.1. Area para Almacenamiento

Los elementos que deben ser almacenados, temporalmente son los siguientes: reactivos USP, envases vacíos nuevos y reusados, material para empaque de productos, producto en espera para el esterilizador, producto en cuarentena y para despacho, combustible para la caldera, agua blanda y agua deionizada.

Los resultados de esta asignación de áreas, se hace bajo las siguientes consideraciones:

	M2	Altura
Reactivos USP = 48 tambores de 50 de alto x 50 cc. diámetro, empacado en tambores de 50 kilos. Existencias para 4 meses (4 x 4)	16	240
Envases de vidrio empacados en cajas de cartón x 25 unidades de 50 ancho x 50 largo x 20 alto. Existencia para 2 meses = 60.000 envases o sean 2.400 cajas (8 x 8)	64	240
Material de empaque y etiquetas-Apilado sobre estibas. Existencia para dos meses (3 x 2 mts.)	6	240
Producto en cuarentena y Despacho. Empacado en cajas de cartón x 25 unidades. Existencia de 1.5 meses (8.0 x 6.0 m^2)	48	240

311.040 ÷ 9 = 34.560 unidades ÷ 25 unidades = 1.382 cajas.

Producto pre-esterilizador. En canastillas de 50 x 70 x 25. Existencia de 0.5 dias (2.50 x 2.50). Número de canastillas = 1.280 frascos ÷ 2 = 640 frascos ÷ 35 frascos = 19 canastillas	6.25	240
Combustible en tanque cilíndrico horizon-		

tal. Capacidad 2.000 galones (3.0 x 3.0) metros	9	260
Agua filtrada en tanque cilíndrico vertical. Capacidad 2.000 galones (2.50 x 3)	10.5	260
Agua blanda - tanque vertical cilíndrico. Capacidad 700 galones (3.0 x 3.0)2	18	260
Agua deionizada - Tanque vertical cilíndrico. Capacidad 1.600 litros (2.0 x 2.0)2	8	260
S U B T O T AL	185.75	

El área total que se requiere para el funcionamiento de esta unidad es de 185.75 metros cuadrados y la altura en promedio será de 2.50 metros.

3.2.2. Areas para Equipo

Se consideran en esta área las secciones para operar los equipos que participan directamente en el proceso de la producción de soluciones desde el acondicionamiento de agua, y reactivo hasta la entrega del producto al consumidor.

Los equipos son: filtro de arena, ablandador, deionizador, ósmosis

inversa, tanques de agua para inyección, mezclador, tanque de soluciones, área estéril, área aséptica, esterilizadores, transporte de soluciones a la selladora, transporte de soluciones a inspección, etiquetado y empaque.

El resultado de la asignación de estas áreas es el siguiente:

	Metros^2
Filtro de Arena:	
cilindro vertical con controles y accesorios para operación y retrolavado (1.0 x 2.0) metros	2
Ablandador:	
cilindro vertical con controles y accesorios (1.0 x 2.0) metros	2
Deionizador:	
cilindros verticales con controles y accesorios (2.0 x 2.0) metros	4
Osmosis Inversa	
Adosado en la pared con controles (1.0 x 2.0)	2
Agua Estéril:	
Conformado por las secciones: áreas prefiltro, filtro, llenadora, tapadora y selladora (2.0 x 3.0) metros	6
Área descarga esterilizador (1.0 x 2.0) metros	2

Area Aséptica	
Conformada por las secciones de: lavado de botellas,	
(5.0 x 2.0) metros	**10**
Preparación de soluciones (3.0 x 4.0) metros	**12**
Cambio de vestuario para operadores (2.0 x 3.0) metro	**6**
Esterilizadores	
Doble puerta para utensilios y producto (2.0 x 2.0)	
metros	**4**
Puerta sencilla para productos (2.0 x 2.0)	**4**
Transportador o Selladora	
Considera el tramo por fuera del área estéril (0.50	
x 2.0)	**1**
Mesa Acumuladora	
Entrega a la selladora (2.0 x 2.5) metros	**5**
Transportador a inspección, etiquetado y empaque	
recibe de canastillas y lleva hasta empaques en	
cajas (4.0 x 3.0)	**12**
S U B T O T A L	**72**

El requerimiento total de área para este servicio es de 72 metros cuadrados, con una altura en promedio de 2.50 metros.

3.2.3. Areas para Administración de la Planta y Control de Calidad

Se tiene en cuenta aquellas unidades del área administrativa que están ligadas al proceso productivo en la fase de planeamiento, dirección, control, supervisión, administración, costos, suministros y despachos.

	Metros2
Dirección de Planta:	
Oficinas para personal técnico (4.5 x 6.0) metros	27
Personal de supervisión (6.0 x 5.5) metros	33
Control de Calidad:	
Laboratorio-Pruebas fisicoquímicas (4.0 x 6.0) metros	24
Pruebas microbiológicas (3.0 x 5.0) metros	15
Administración:	
Oficinas para directivos	60
Oficinas para contabilidad y costos	90
Oficinas para administración de personal	20
Oficina para suministros y despachos	30
T O T A L	299

Esta área de apoyo administrativo necesita una extensión de 299 metros cuadrados y una altura promedio de 2.50 metros.

3.2.4. Area para Servicios, Pasillos y Accesos

Los elementos que hacen parte de esta repartición son los siguientes: calderas, compresor de aire, subestación eléctrica, calentador de agua blanda, filtro para aire comprimido, filtro para vapor condensado, acondicionador de aire, taller de mantenimiento de reparación y prevención, pasillos para transporte interno y circulación de personas, parqueadero de vehículos, vias de acceso a las bodegas para carga y descarga y filtro para vapor.

Resultado de esta asignación es el cálculo siguiente:

	Metros^2
Caldera:	
Cuerpo cilíndrico horizontal, bombas y controles laterales (3.0 x 2.0) metros	6
Compresor de Aire:	
Bloque montado sobre tanque cilíndrico horizontal (1.50 x 1.0) metros	1.5
Subestación Eléctrica:	
Transformador trifásico con tablero de control	

(2.0 x 2.0) metros	4.0
Calentador de Agua Blanda:	
Intercambiador de tubos y carcaza conectado a la línea de agua blanda	1.4
Filtro para Vapor:	
Soporte y filtro de discos conectado a la línea de vapor (0.9 x 1.5) metros	1.4
Filtro para Aire:	
Soporte y filtro de disco conectado a la línea de aire (0.9 x 1.5) metros	1.4
Filtro para Condensado:	
Soporte y filtro de profundidad (0.9 x 1.5) metros	1.4
Acondicionamiento de Aire:	
Unidad centralizada para área estéril, área aséptica y oficinas (5 x 4) metros	20.0
Ductos de Aire (0.4 x 30) metros	12.0
Taller de mantenimiento arreglos menores (5.0 x 7.0) metros	35.0
Pasillos para transporte interno, para manejo de material y tráfico de personas (20% de área de	

almacén y equipos)	52.0
Servicios sanitarios (3.0 x 3.0) metros	9.0
Parqueaderos 20% del acumulado (701.85)	141.0
Acceso a Bodegas 15% acumulado (701.85)	106.0
T O T A L	392.10

3.2.5. Areas para Zonas Libres y Esparcimientos

Aquí se plantea la necesidad de crear un buen ambiente de trabajo, que rompa la monotonía del paisaje y estimule al personal. Las unidades correspondientes son: cafetería, cambio de ropas y zonas verdes.

La asignación de estas áreas son las siguientes:

	Metros^2
Cafetería (6.0 x 6.0) metros	36
Cambio de ropas (6.0 x 6.0) metros	36
Zonas verdes: en los espacios que rodean la planta 30% del acumulado (1.020.75) metros^2	306
S U B T O T A L	378

Con la información ya procesada antes, en la cual se conocen las diferentes actividades que conforman el proceso productivo, se debe

aglutinar en un todo armónico y funcional, con el fin de lograr el planeamiento de la distribución de la planta.

A partir de un esquema básico se va ordenando, bajo una secuencia lógica y de acuerdo al flujo normal de los materiales, cada una de las operaciones o actividades que conforman el proceso total, reajustando este esquema básico y mejorando su ordenamiento se va llegando a la distribución adecuada.

Al integrar las áreas, se busca una visión de conjunto, totalizando las áreas determinadas en el punto anterior y encontramos así que el área mínima requerida será:

	Metros^2
Area de almacenamiento	185.75
Area de Equipo u operación	72.00
Area de administración y control de calidad	299.00
Area para servicios, pasillos y accesos	392.10
Area para zonas libres y esparcimiento	378.00
AREA MINIMA TOTAL	1.326.85

La nueva fábrica necesita como área mínima construida 1.326.85 me-

tros cuadrados, según el proceso que se ha descrito anteriormente en la asignación de espacios, en el cual se contempla la construcción de las instalaciones y se reservan zonas libres. Considerando una posible ampliación de esta fábrica se recomienda adquirir un terreno de 5.000 metros cuadrados o sea media hectárea.

El procedimiento descrito nos lleva al esquema definitivo que es el recomendado para la planta en proyecto y que está representado en el Plano 3.

3.3. Productos a Elaborar

En los términos de referencia que se ha establecido en el presente estudio, se plantea la elaboración de los siguientes productos en presentación de 500 cc para que el programa de fabricación se ajuste a dicha línea:

Dextrosa al 5% en agua destilada

Dextrosa al 5% mas cloruro de sodio al 0.45% en agua destilada

Dextrosa al 5% mas cloruro de sodio al 0.9% en agua destilada

Dextrosa al 10% en agua destilada

Dextrosa al 10% en solución salina

Cloruro de Sodio

Solución de Hartman

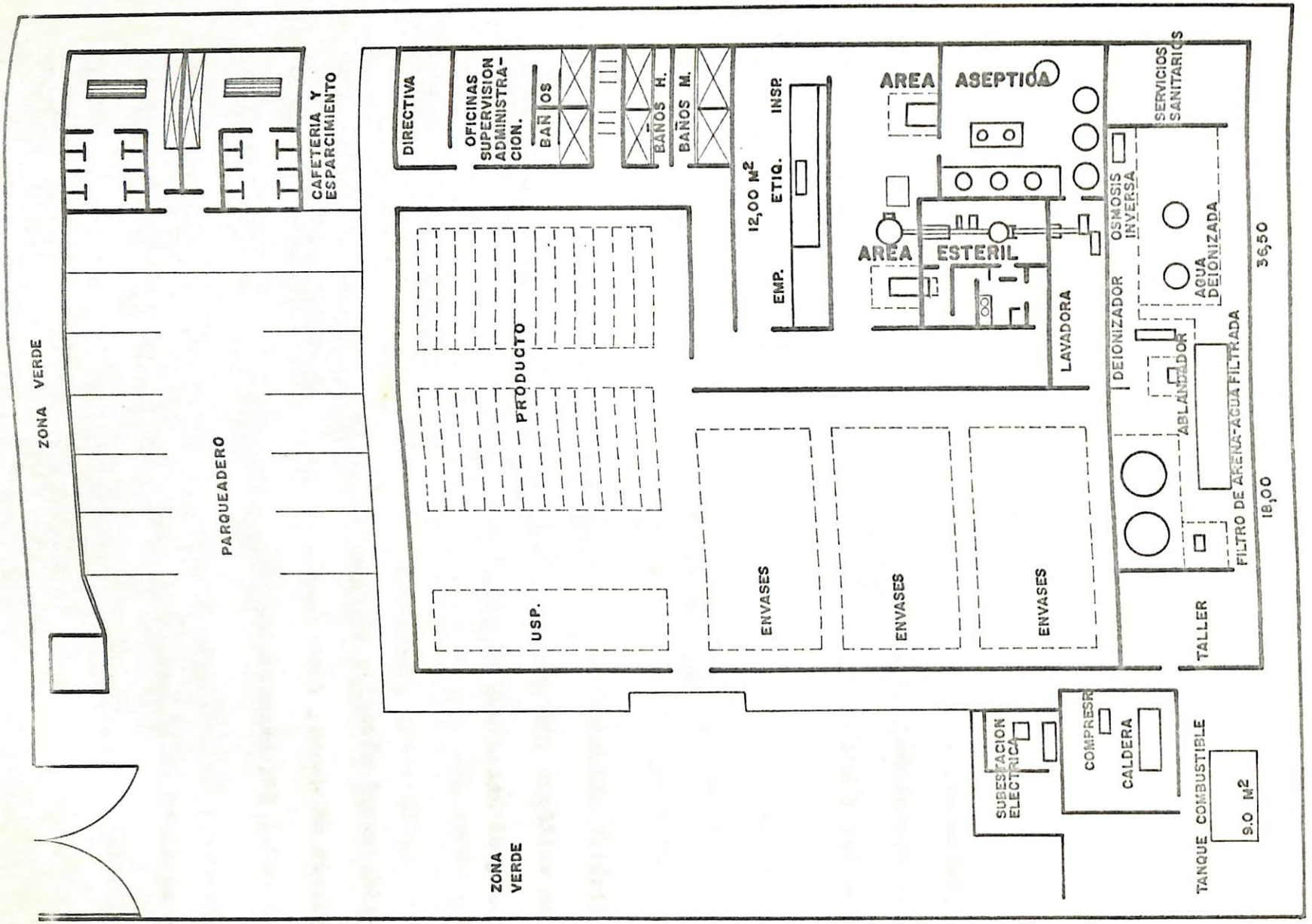
Solución de Ringer

Plano : 3

PLANTA PRODUCTORA DE DEXTROSAS Y ELECTROLITOS

DISTRIBUICION GENERAL DE LA PLANTA FISICA

PASTO —— 1.983



FUENTE : Esta Investigación

Suero Fisiológico

Agua Estéril

3.4. Definición y Formulación Normalizada de Productos

Para la descripción normalizada de cada uno de estos productos, se tomará en cuenta lo expuesto en la Unites States Pharmacopea XX (USP XX), y con base en ella, se establecerá la formulación y las normas de calidad que deben cumplir.

3.4.1. Inyección de Dextrosa al 5% en Agua

- Formulación. La inyección de dextrosa es una solución estéril de Dextrosa (calidad USP) en agua para inyección, que contiene no menos del 95% y no mas del 105% de la cantidad declarada de glucosa. ($C_6 H_{12} O_6$) y agua (H_2O)

De acuerdo a esta definición cada litro de solución inyectable debe contener mínimo (47.5) gramos y máximo 52.5 gramos de dextrosa, para un contenido nominal de 50 gramos de Dextrosa por 1.000 cc. de solución.

La formulación para elaborar 1 litro de inyección de dextrosa al 5% en agua será:

Dextrosa (USP)	50 gramos
Agua para inyección	0.9717 litros

- Normas de calidad. La inyección de dextrosa al 5% en agua debe cumplir las siguientes normas de calidad:

Prueba de Pirógenos. De acuerdo a lo descrito en la USP XX, Prueba 151.

Ph. Entre 3.5 y 6.5 de acuerdo a la norma USP XX, prueba 151.

Ph. entre 3.5 y 6.5 de acuerdo a la norma USP XX, prueba 791.

Metales pesados, límite = 0.0005 C, en la cual C es la cantidad en gramos de dextrosa contenidas en la inyección. De acuerdo con la norma USP XX, prueba 231.

Prueba de esterilidad. De acuerdo a la norma USP XX, prueba 71.

Para inyecciones. De acuerdo a la norma USP XX, prueba 1.

Para composición. De acuerdo a la norma USP XX, pág. 218.

3.4.2. Inyección de Dextrosa al 10% en Agua

- Formulación. La inyección de dextrosa es la solución estéril de dextrosa (calidad USP) en agua para inyección, que contiene no menos del 95% y no mas del 105% de la cantidad declarada de glucosa ($C_6 H_{12} O_6$) - Agua (H_2O).

De acuerdo a esto, cada litro de solución inyectable debe contener mínimo 95.0 gr. y máximo 105 gr. de dextrosa, para un contenido nominal de 100 gr. de dextrosa por 1.000 cc.de solución.

La formulación para elaborar un litro de inyección de dextrosa al 10% en agua será:

Dextrosa (USP) 100 gr.

Agua para Inyección 0.9426 litros

- Normas de Calidad. La inyección de dextrosa al 10% en agua debe cumplir las siguientes normas de calidad:

Para pirógenos. De acuerdo a la norma USP XX, prueba 151

Ph entre 3.5 y 6.5 de acuerdo a la norma USP XX prueba 791.

Metales pesados. Límite = 0.0005 C, en el cual C es la cantidad en gramos de dextrosa, contenidas en la inyección. De acuerdo a la norma USP XX, prueba 231.

Para esterilidad. De acuerdo a la norma USP XX, prueba 71.

Para inyecciones. De acuerdo a la norma USP XX, prueba 1.

Para composición. De acuerdo a la norma USP XX, Pag. 218.

3.4.3. Inyección de Dextrosa al 5% y Cloruro de Sodio al 0.9% en Agua

- Formulación. La inyección de dextrosa y cloruro de sodio es una solución estéril de dextrosa y cloruro de sodio en calidad USP en agua para inyección, que contiene no menos del 95% y no mas del 105% de la cantidad declarada de glucosa ($C_6 H_{12} O_6$) - Cloruro de Sodio (NaCl).

De acuerdo a esta definición, cada litro de solución inyectable debe contener mínimo 47.5 gr. y máximo 52.5 gr. de dextrosa y mí-

nimo 8.55 y máximo 9,45 grs. de cloruro de sodio, para un contenido nominal de 50 gr. de dextrosa y 9 gr. de cloruro de sodio por 1.000 de solución.

La formulación para elaborar un litro de inyección de dextrosa al 5% y cloruro de sodio al 0.9% en agua será:

Dextrosa (USP)	50 gr.
Cloruro de sodio (USP)	9 gr.
Agua para inyección	0.9691 litros

- Normas de Calidad. La inyección de dextrosa al 5% y cloruro de sodio al 0.9% en agua debe cumplir las siguientes normas de calidad:

Prueba de Pirógenos. De acuerdo a la norma USP XX, prueba 151.

Ph. entre 3.5 y 6.5, de acuerdo a la norma USP XX, prueba 791.

- Ferrocianuro. De acuerdo a la norma USP XX, pág. 219.

Para esterilidad. De acuerdo a la norma USP XX, prueba 71.

Para inyecciones. De acuerdo a la norma USP XX, prueba 1.

Para composición. De acuerdo a la norma USP XX, pág. 219.

3.4.4. Inyección de Dextrosa al 5% y Cloruro de Sodio al 0.45% en Agua

- Formulación. La inyección de dextrosa y cloruro de sodio es una solución estéril de dextrosa mas cloruro de sodio en calidad USP

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BIBLIOTECA Y DOCUMENTACION

en agua para inyección, que contiene no menos del 95% y no mas del 105% de la cantidad declarada de glucosa ($C_6 H_{12} O_6$) y cloruro de sodio (NaCl).

De acuerdo a esta definición, cada litro de solución inyectable debe tener mínimo 47.5 gr. y máximo 52.5 gr. de dextrosa y mínimo 4.30 y máximo 4.70 gr. de cloruro de sodio, para un contenido nominal de 50 gr. de dextrosa y 9 gr. de cloruro de sodiopor 1.000 cc. de solución.

La formulación para elaborar un litro de inyección de dextrosa al 5% y cloruro de sodio al 0.45% en agua será:

Dextrosa (USP)	50 gr.
Cloruro de sodio (USP)	4.5 gr.
Agua para inyección	0.9715 litros

- Normas de calidad. La inyección de dextrosa al 5% y cloruro de sodio al 0.45% en agua debe cumplir las siguientes normas de calidad:

Prueba de Pirógenos. De acuerdo a la norma USP XX, prueba 151.

Ph entre 3.5 y 6.5, de acuerdo a la norma USP XX, prueba 791.

Ferrocianuro. De acuerdo a la norma USP XX, pág. 219.

Para esterilidad. De acuerdo a la norma USP XX, prueba 71.

Para inyecciones. De acuerdo a la norma USP XX, prueba 1.

Para composición. De acuerdo a la norma USP XX, pág. 219.

3.4.5. Inyección de Cloruro de Sodio al 0.9% en Agua

- Formulación. La inyección de cloruro de sodio es una solución estéril de cloruro de sodio (calidad USP) en agua para inyección, que contiene no menos del 95% y no mas del 105% de la cantidad declarada de NaCl.

De acuerdo a lo definido, cada litro de solución inyectable debe contener mínimo 8.55 gr. y máximo 9.45 gr. de cloruro de sodio, para un contenido nominal de 9 gr. de cloruro de sodio por 1.000 cc. de solución.

La formulación para elaborar 1 litro de inyección de cloruro de sodio al 0.9% en agua será:

Cloruro de sodio (USP) 9 gr.

Agua para inyección

- Normas de Calidad. La inyección de cloruro de sodio al 0.9% en agua debe cumplir las siguientes normas de calidad:

Prueba de pirógenos. De acuerdo a la norma USP XX, prueba 151.

Ph entre 3.5 y 6.5, de acuerdo a la norma USP XX, prueba 791.

Ferrocianuros. De acuerdo a la norma USP XX, pág. 219.

Para esterilidad. De acuerdo a la norma USP XX, prueba 71.

Para inyecciones. De acuerdo a la norma USP XX, prueba 1.

Para composición. De acuerdo a la norma USP XX, pág. 219.

3.4.6. Inyección de Ringer

- Formulación. La inyección de Ringer es una solución estéril de cloruro de sodio (calidad USP), cloruro de potasio (calidad USP) y cloruro de calcio (calidad USP) en agua para inyección.

En 100 ml. de solución debe contenerse:

No menos de 323 mg y no mas de 354 mg de sodio (equivalente a no menos de 820 mg y no mas de 900 mg de cloruro de sódio).

No menos de 14.9 mg y no mas de 16.5 mg de potasio (equivalente a no menos de 28.5 mg y no mas de 31.5 mg de cloruro de potasio.

No menos de 8.2 mg y no mas de 0.9 mg de calcio (equivalente a no menos de 30 mg y no mas de 36 mg de cloruro de calcio dihidratado).

No menos de 523 mg y no mas de 500 mg de cloruro (como cloruro de sodio, cloruro de potasio y cloruro de calcio dihidratado).

La formulación para elaborar un litro de inyección de Ringer es:

Cloruro de sodio (USP)	8.60 gr.
Cloruro de potasio (USP)	0.30 gr.
Cloruro de calcio (USP)	0.30 gr.
Agua para inyección	0.9974 litros

- Normas de Calidad. La inyección de Ringer debe cumplir las siguientes normas de calidad:

Para Pirógenos. De acuerdo a la norma USP XX, prueba 151.

Ph entre 5.0 y 7.5, de acuerdo a la norma USP XX, prueba 791.

Arsénico. Límite = 0.08 PPM de acuerdo a la norma USP XX, prueba 211.

Ferrocianuros. De acuerdo a la norma USP XX, pág. 219.

Metales pesados. Límite = 0.3 PPM, de acuerdo a la norma USP XX, prueba 231.

Para esterilidad. De acuerdo a la norma USP XX, prueba 71.

Para inyecciones. De acuerdo a la norma USP XX, prueba 1.

Para composición. De acuerdo a la norma USP XX, pág. 711 y 712.

3.4.7. Inyección de Hartman

- Formulación. La inyección de Hartman o de Ringer (lactosada) es una solución estéril de cloruro de calcio (calidad USP), cloruro de potasio (calidad USP), cloruro de sodio (calidad USP) y lactato de sodio (calidad USP) en agua para inyección.

En 100 ml de solución se debe contener:

No menos de 285 mg y no mas de 315 mg de sodio (como cloruro de sodio y lactato de sodio).

No menos de 14.1 mg y no mas de 17.3 mg de potasio (equivalente a no menos de 27 mg y no mas de 33 mg de cloruro de potasio).

No menos de 4.9 mg y no mas de 6.0 mg de calcio (equivalente a no menos de 18 mg y no mas de 22 mg de cloruro de calcio dihidratado).

No menos de 368 mg y no mas de 408 mg de cloruro (como cloruro de sodio, cloruro de potasio y cloruro de calcio dihidratado).

No menos de 231 mg y no mas de 261 mg de lactato (equivalente a no menos de 290 mg y no mas de 330 mg de lactato de sodio).

La formulación para elaborar un litro de inyección de Hartman es:

Cloruro de Sodio (USP)	6.01 gr.
Cloruro de Potasio (USP)	0.30 gr.
Cloruro de Calcio dihidratado (USP)	0.20 gr.
Lactato de Socio (USP)	3.10 gr.
Agua para inyección	0.9974 litros

Normas de Calidad. La inyección de Hartman debe cumplir las siguientes normas de calidad:

Para Pirógenos. De acuerdo a la norma USP XX, prueba 151.

Ph entre 6.0 y 7.5 de acuerdo a la norma USP XX, prueba 791.

Arsénico. Límite = 0.08 PPM, de acuerdo a la norma USP XX, prueba 211.

Ferrocianuro. De acuerdo a la norma USP XX, pág. 219.

Metales pesados. Límite = 9.3 PPM, de acuerdo a la norma USP XX, prueba 231.

Para esterilidad. De acuerdo a la norma USP XX, Prueba 71.

Para inyecciones. De acuerdo a la norma USP XX, prueba 1.

Para composición. De acuerdo a la norma USP XX, pág. 711 y 712.

3.4.8. Suero Fisiológico

- Formulación. La inyección de suero fisiológico es una solución estéril de cloruro de sodio (calidad USP) en agua para inyección, que contiene no menos del 95% y no mas del 105% de la cantidad declarada de cloruro de sodio y agua estéril.

De acuerdo a esta definición cada litro de solución inyectable debe contener mínimo 42.5 gr y máximo 47.5 gr de cloruro de sodio, para un contenido nominal de 45 gr de cloruro de sodio por 1.000 cc de solución.

La formulación para elaborar 1 litro de inyección de suero fisiológico será:

Cloruro de sodio	45 gr
Agua para inyección	0.9745 litros

- Normas de Calidad. La inyección de suero fisiológico debe cumplir las siguientes normas de calidad:

Prueba de Pirógenos. De acuerdo a la norma USP XX, prueba 151.
Ph entre 3.5 y 6.5, de acuerdo a la norma USP XX, prueba 791.
Ferrocianuros. De acuerdo a la norma USP XX, pág. 219.
Para esterilidad. De acuerdo a la norma USP XX, prueba 71.
Para inyecciones. De acuerdo a la norma USP XX, prueba 1.
Para composición. De acuerdo a la norma USP XX, pág. 219.

3.4.9. Agua Estéril

- Formulación. El agua estéril es el producto de la destilación, el cual se considera prácticamente libre de pirógenos, sustancias absolutamente nocivas en el caso de ser inyectadas intravenosamente. En este estado corresponde al agua que se utiliza en la solución de líquidos electrolíticos señalados en las páginas anteriores de este capítulo.

- Normas de Calidad. El agua estéril debe someterse a las siguientes normas de calidad:

Prueba de Pirógenos. De acuerdo a la norma USP XX, prueba 151.

Ph entre 3.5 y 6.5, de acuerdo a la norma USP XX, prueba 791.

Prueba de esterilidad. De acuerdo a la norma USP XX, prueba 71.

Prueba para inyecciones. De acuerdo a la norma USP XX, prueba 1.

Para composición. De acuerdo a la norma USP XX, pág. 219.

3.5. Requerimientos de Materia Prima e Insumos

Con el fin de establecer la capacidad de cada uno de los equipos, así como de los requerimientos de servicios (agua, energía, combustibles, etc.) se tomó como referencia la producción diaria que para el primer año es de 1.280 unidades de 500 cc. de solución que multi-

plicado por 243 dias al año se obtiene un volumen de 311.040 unidades de 500 cc de solución por año, para el último año de vida útil del proyecto la producción diaria requerida será de 2.200 unidades.

La jornada laboral será de 48 horas semanales.

3.5.1. Consumo de Agua en el Proceso

Base: 1 año de 243 dias

Producción anual: 311.040 unidades de producto de 500 cc.

Unidades de producción diaria: 1.280

Volumen de agua en solución (aproximadamente) = 640 litros

Suponiendo que pueden existir pérdidas del 20% en agua para inyección debido a la evaporación, drenajes, fujas, etc. se determina la cantidad de agua necesaria diariamente:

Volumen de agua en solución = 640 litros x 1.2 = 748 litros; 196 galones dia.

Se necesitan 20 galones por hora de agua para inyección en una de las estaciones de lavado de botellas, la cual trabaja 8 horas diarias, por lo tanto el equivalente de ósmosis inversa debe producir mínimo 196 + 20 x 8 = 356 galones por dia de agua para inyección, es decir 1.346 litros por dia.

El equipo de ósmosis inversa produce continuamente 24 horas al dia agua para inyección. La capacidad mínima requerida para este equipo es de 60 litros por hora. Los equipos se consiguen comercialmente con capacidad para 100, 125, 250, 500 y 1.000 litros por hora, por lo tanto, el equipo de ósmosis inversa necesario inicialmente para producir 311.040 unidades al año es el que produce 100 litros por hora.

Cuando la planta duplique la producción, como es la meta al cabo del décimo año de vida útil del proyecto, su capacidad deberá también duplicarse, se descarta comprar desde el comienzo un equipo de mayor capacidad debido a sus elevados costos y a la utilización de mayor espacio y por lo tanto a la subutilización de la capacidad del equipo. Este equipo propuesto irá adosado a la pared y usará como alimento, agua deionizada proveniente del tanque de almacenamiento de agua deionizada.

En el diagrama 8, se muestran las unidades principalmente tanques de almacenamiento, donde se acumula o fluye el agua, con la identificación del tipo de servicio que se presta, con base en este diagrama se presenta a continuación las necesidades del agua.

3.5.1.1. Equipo de Osmosis Inversa

A este equipo entra el flujo 10, de agua deionizada, produce un flujo

de agua para inyección 9 que se conduce al tanque respectivo y un rechazo, flujo 11 que se retorna al tanque de almacenamiento de agua deionizada. El equipo 9 utiliza dos galones por cada 1.1 galón de agua para inyección producida, por lo tanto:

Flujo 10 = 100 x 2/11 = 182 LPH x 24H/3.78 = 1.156.0

Flujo 11 = 182 - 100 = 82 LPH x 24H/3.78Lx6 = 520.6

Flujo 9 = 100 LPH x 24H/3.78 = 635

3.5.2. Almacenamiento de Agua para Inyección

Al almacenamiento de agua para inyección entra el flujo 9 y salen los flujos 6 para la lavadora de botellas, 12 para elaborar la solución electrolítica y 15 para enjuagues de equipo y 18 el sobrante de agua no utilizada (ver Diagrama 8).

Flujo 6: este flujo se usa en la séptima estación de la lavadora de botellas para asegurar la limpieza total de ellas, su consumo de acuerdo con la máquina lavadora seleccionada es de 30 galones por hora. La lavadora trabaja 8 horas diarias.

Flujo 6: 20 x 8 = 160 G.P.D.

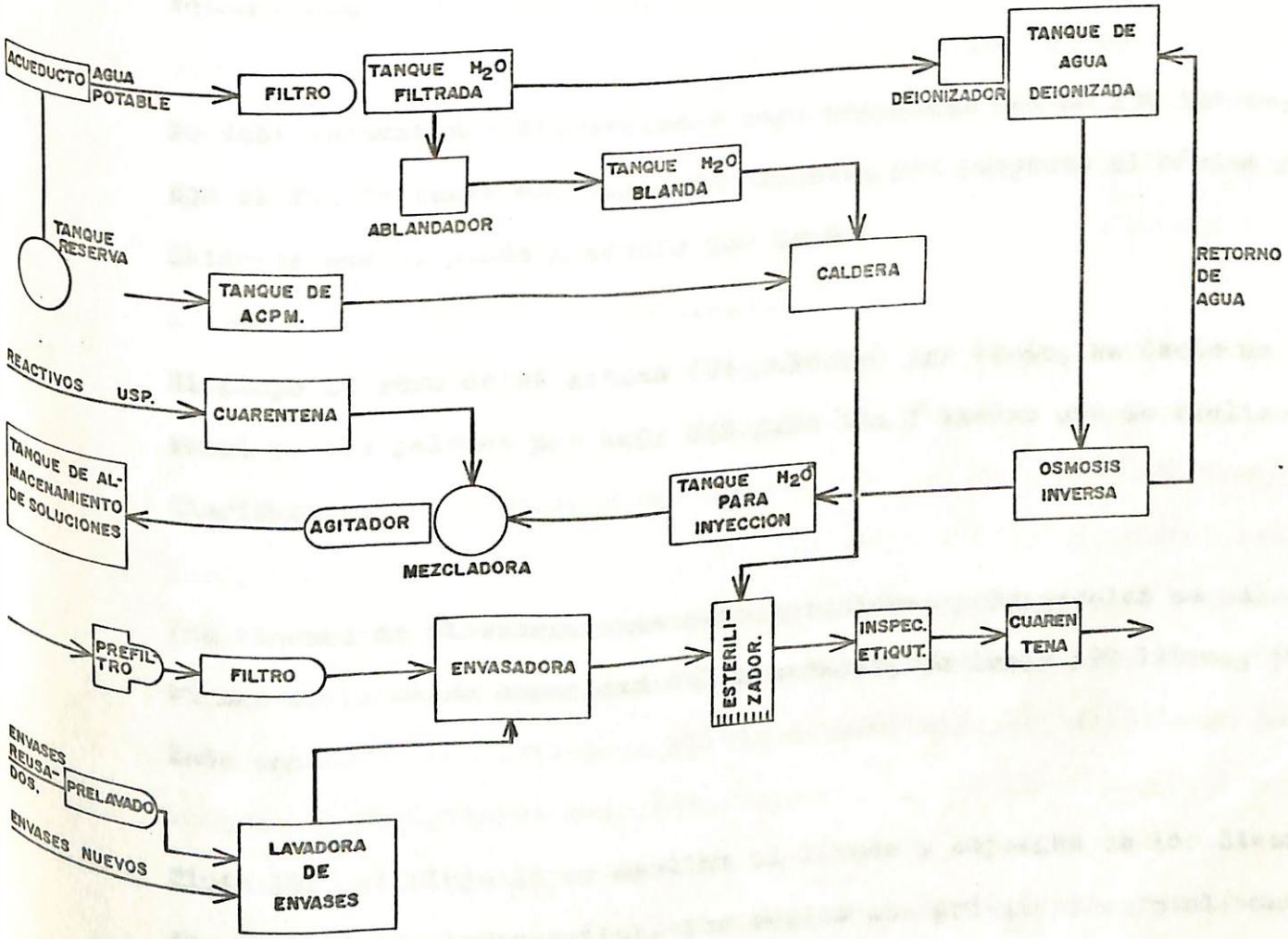
Flujo 12: el flujo 12 es el que se envía al tanque de mezclado para la preparación de los productos. Su magnitud depende de la capacidad de este tanque, la cual se determina a continuación:

Diagrama.: 8

PLANTA PRODUCTORA DE DEXTROSAS Y ELECTROLITOS

PROCESO DE PRODUCCION

PASTO —— 1.983



FUENTE: Esta investigación.

Número de unidades a producir diariamente 1.280 x 500 cc.

Tiempo estimado de duración total del mezclado = 1 hora

Número de operaciones de mezclado cada día de trabajo (Jornada de 8 horas) = 7

Unidades producidas por cada tanda: 183 x 500 cc.

Volumen de agua empleada: 183 x 0.5 litros: 92 litros

Volumen libre sobre solución 20% = 18 litros

Volumen mínimo del mezclador = 110 litros

Se debe seleccionar un mezclador cuya capacidad sea de 130 litros, con el fin de tener un márgen de amplitud con respecto al máximo de unidades que se puede producir por tanda.

El flujo 12 será de 92 litros (24 galones) por tanda, es decir un total de 169 galones por cada día para las 7 tandas que se realizan diariamente.

Los tanques de almacenamiento para soluciones parenterales se seleccionan de la misma capacidad del mezclador, es decir 130 litros, por cada uno.

Flujo 15: el flujo 15 se destina al lavado y enjuague de los diversos equipos que lo necesitan, los cuales son principalmente el tanque de mezcla, los tanques de almacenamiento de soluciones parente-

rales y la lavadora de frascos. Se estimó el consumo diario para estas operaciones de 20 galones.

Flujo 18: puesto que no es conveniente usar agua de inyección que haya estado depositada mas de 24 horas se propone la consecución de dos tanques de agua para inyección cada uno de los cuales trabajaría durante 24 horas. En esta forma un tanque se llenaría con el agua que se va a usar al dia siguiente mientras el otro tanque está suministrando el agua necesaria para la operación en ese dia y así sucesivamente. El flujo 18 es el agua sobrante diaria, la cual se retorna al tanque de agua deionizada.

Flujo 18 = Entra - Sale

Entra = (flujo 9) 635 G.P.D.

Sale = Flujo 6 + 12 + flujo 15 =

160 + 169 + 20 = 349 G.P.D.

Flujo 18 = 286 galones por dia

Con el consumo total de agua para inyección de 635 galones por dia, se dimensionan los tanques de almacenamiento de agua para inyección. Para mantener una reserva de un dia de operación se seleccionan dos tanques de 700 galones cada uno.

Cuando se haga la expansión de la planta al doble de su capacidad se deben adquirir dos nuevos tanques de almacenamiento de lamisma capacidad anterior.

3.5.3. Almacenamiento de Agua Deionizada

El agua deionizada se usa como alimento al equipo de ósmosis inversa, flujo 10, alimento a las estaciones 5a. y 6a. de la lavadora de envases flujo 5. El almacenamiento recibe el retorno del equipo de ósmosis inversa (flujo 11), el sobrante diario de agua para inyección (flujo 18) y el agua tratada en el equipo deionizador (flujo 17). Este flujo permite estimar la capacidad del equipo deionizador.

Flujos de salida: 20 G.P.H. x 2 estaciones x 8 horas = 320 G.P.D.

Flujo 10 : = 1.156 G.P.D.

Total Salida = 1.476 G.P.D.

Flujos de entrada:

Flujo 11 : = 520 G.P.D.

Flujo 18 : = 286 G.P.D.

Total de entrada : = 806 G.P.D.

Por lo tanto el deionizador debe procesar la diferencia entre entrada y salida 669 G.P.D. El almacenamiento de agua deionizada se estima en 1.600 galones en dos tanques cada uno de 800 galones que aseguren reservas suficientes para uso en la planta.

3.5.4. Almacenamiento de Agua Blanda

Agua blanda se usa para alimentar la caldera que produce vapor para esterilizar (flujo 7), para alimentar una vez precalentada la torcera estación de lavadora de frascos (flujo 1) y como fluido frio para el enfriamiento de las autoclaves (flujo 4). Al almacenamiento llega el agua del ablandador (flujo 16), el retorno de condensado de la autoclave (flujo 20) y agua caliente de los enfriadores rápidos de las autoclaves (flujo 3).

Antes de proceder a establecer la magnitud de almacenamiento de agua blanda es necesario hacer la selección de la caldera de acuerdo con las necesidades de esterilización de la planta.

3.5.5. Capacidad de Esterilización - Seleccion Autoclaves

La capacidad de esterilización depende de la producción diaria de soluciones.

Unidades de producto diario 1.280

Unidadades producidas por tanda mezclador 183 botellas

Dimensión de la botella: 8 cms. de diámetro x 19 cms. de alto

Peso aproximado de la botella llena: 1 kilogramo.

Las botellas para ser sometidas a esterilización se colocan en canastillas de acero inoxidable, las cuales una vez montadas en un carro transportador se introducen a la autoclave. Dado que las canastillas se manejan por operarios el peso de cada una de ellas se considera que debe ser de 35 kilogramos.

Número de botellas por canastilla: 35

Dimensiones de la canastilla: (50 x 70 x 25) cms.

Debido a los altos costos que tienen las autoclaves y a la necesidad de obtener dos de ellas para asegurar funcionamiento normal de la planta, se tienen en cuenta los siguientes criterios:

Las autoclaves deben trabajar el mayor número de horas posibles, lo cual disminuye su capacidad pero decrecen los costos de operación de la caldera.

Para rebajar costos no se consideran autoclaves de apertura automática sino manual.

Para que las autoclaves sean de amplio uso se selecciona el grupo que posee tiempo de esterilización ajustable, control de temperatura entre 121 y 135°C y facilidades de secado y vacío.

Con base en estos criterios se seleccionan dos esterilizadores. Es importante que uno de ellos sea de una puerta y otro de dos puertas, una frontal y otra posterior. Este último a mas de utilizarse para

esterilizar productos terminados se destinará en parte a la esterilización de materiales que deben entrar a la zona estéril con la cual estará comunicada.

Cada autoclave tiene los siguientes requerimientos de servicios: consumo de agua en el enfriador rápido 3 galones por minuto, consumo de vapor 110 libras por hora máxima, electricidad 120 voltios monofásico, 15 amperior y 60 Hz.

Cada autoclave posee una trampa de vapor por la cual se obtiene un condensado el cual se puede recircular al almacenamiento de agua blanda (flujo 20). Asumiendo la recuperación total de vapor

Flujo 20: 110 libras vapor/esterilización x 10 esterilizaciones

880 libras/dia/62.4 Llb/Ft3 = 17.6 galones dia

8 esterilizaciones para producción y 2 para zona estéril y servicios generales.

Con base en esta selección de autoclaves se establece que se pueden esterilizar simultáneamente 5 canastillas conteniendo cada una de ella 35 botellas.

Botellas esterilizadas por tanda: 175

Número de esterilizaciones diarias para producto: $\frac{1.280}{175}$ = 8 tandas

Tiempo estimado de duración de cada esterilización: 1 hora.

3.5.6. Selección de la Caldera

Con base en la capacidad esterilizadora que se determinó en la sección anterior, se puede establecer el consumo de vapor necesario para la planta.

Debido a que la adquisición de la caldera es una inversión fija y va a servir para las etapas de expansión de la planta, se considera que su capacidad debe ser 20 BHP que produce 690 libras de vapor por hora. La caldera seleccionada corresponde al tipo pirotubular, tiene un consumo de combustible ACPM de 6 galones por hora.

Se calcula el flujo 7:

690 lbs/hora/62.4 lbs/Pt3 = 11.1 Pt3 x 7.48 = 83.16 por hora

3.5.7. Tanque de Almacenamiento de Combustible

La caldera debe poseer un almacenamiento de ACPM que asegure su operación continua. Generalmente se considera conveniente dispone de una reserva para un mes de consumo

Capacidad de almacenamiento máximo: 6 G.P.H. x 8 horas x 21 dias = 1.008 galones

Selecciona un tanque de 2.000 galones.

3.5.8. Consumo de Agua para Enfriamiento Rápido de Esterilizador

Al final del ciclo de esterilización se procede a hacer un enfriamiento rápido de la autoclave, lo cual evita que las botellas al salir del equipo estallen violentamente. El consumo máximo de agua blanda (flujo 4) se estima de la siguiente forma:

Flujo máximo de agua: 3 galones por minuto

Tiempo estimado de duración del enfriamiento: 10 minutos/esterilización.

Esterilizaciones por dia (máximo): 20

Flujo 4: 3 x 10 x 20 : 600 GPD máximo

3 x 10 x 10 : 300 GPD mínimo

El flujo 3 de retorno del condensador es exactamente igual.

De esta forma se puede establecer la capacidad de almacenamiento de agua blanda.

Entrada:

Flujo 20: 17.6 G.P.D.

Flujo 3: $\frac{300}{317.6}$ G.P.D (mínimo)

Salida:

Flujo 7 : 83.1 G.P.D. x 8 = 664.8 G.P.D.

Flujo 1 : 160 G.P.D. (20 GPH x 8 horas)

Flujo 4 : $\frac{300}{1.124.8}$ GPD

Lo que entra menos lo que sale determina el consumo y la capacidad de ablandador (flujo 16).

Flujo 16: 807.1 G.P.D.

En orden a economizar energía proveniente del enfriamiento de esterilización (flujo 3) este flujo debe entrar al mismo tanque del cual se alimenta la caldera, precalentado así el flujo 7, aumentando la eficiencia de la caldera. El flujo 4 se conecta a otro tanque de almacenamiento.

El almacenamiento se diseña con dos tanques cada uno 700 galones, debido a que se ha considerado la caldera trabajando a máxima carga. Lo anterior en base a que el total de agua que recibe el tanque de agua blanda es de 1.124.8 G.P.D.

3.5.9. Almacenamiento de Agua Potable Filtrada

Al tanque de agua potable entra el flujo 19 proveniente del filtro de arena y el flujo 21, el cual conecta el drenaje de la estación tercera, cuarta, quinta, sexta y séptima de la lavadora de envase mas la estación de lavado externo. De este tanque sale el flujo 16, alimento del ablandador, 17 alimento del deionizador, 13 para lavado del filtro de arena, 14 para la segunda estación y para la estación externa de la lavadora de envase así como también para la lava-

dora de tapones.

Sale:

Flujo 16: 807.1 G.P.D.

Flujo 17: 669 G.P.D.

Flujo 13: Estimado 3 G.P.D.

Flujo 14: 30 x 2 x 8 + 20 = 340 G.P.D.

Total : 1.819.1

Entra:

Flujo 21: 5 estaciones x 20 x 8 h = 800

Flujo 19: Salida - Entra = 1.019.1

Se selecciona para almacenamiento un tanque de agua potable de 2.000 galones, en cuanto a filtro de arena, éste debe procesar 2 galones por minuto de agua potable de la red municipal.

3.6. Balance de Sólidos

En esta sección se procede a hacer el balance de sólidos necesarios para la producción de las soluciones electrolíticas tomando como base la capacidad de la planta para 311.040 unidades anuales de 500 cc. cada una. De acuerdo a la participación porcentual del consumo, se procede a calcular los niveles de producción inicial por nombre del producto para el año uno. (ver Cuadro 12)

Cuadro 12

PARTICIPACION PORCENTUAL DE PRODUCTO OBSERVADO EN 1981

Y PROYECCION DE LA DEMANDA PARA EL AÑO 1985

No. ORDEN	NOMBRE DEL PRODUCTO	CONSUMO	%	CONSUMO PROYECTADO
1	Dextrosa al 5% x 500 cc.	104.617	49.52	154.027
2	Dextrosa al 5% + cloruro de sodio al 0.45% Fco. 500 cc.	923	0.43	1.337
3	Idem + cloruro de sodio al 0.9%	33.152	15.69	48.802
				204.166
4	Dextrosa al 10% en Ad x 500 cc.	9.318	4.41	13.717
5	Dextrosa al 10% en sn x 500	2.246	1.06	3.297
				17.014
6	Lactato de sodio x 500 cc.	257	0.13	404
7	Solución Hartman x 500	23.526	11.14	34.650
8	Solución Ringer x 500	27.830	13.17	40.964
9	Suero fisiológico x 500	5.495	2.60	8.087
10	Agua estéril x 500	3.913 *	1.85	5.755
	T O T A L	211.277	100	311.040

FUENTE: Esta Investigación

* Se suman: Bicarbonatos + Dextrosa al 33% reducidos a frascos x 500 cc.

3.7. Requerimientos de Reactivos Químicos

A continuación se presenta el balance de reactivos químicos calidad U.S.P. el cual se hace con base en la composición de productos. 6/

Dextrosa U.S.P.

En solución al 5%	204.166 x 25 gr ÷ 1.000	= 5.104.15 Kgs
En solución al 10%	17.014 x 50 gr	= 850.70 Kgs
		5.954.85 Kgs

Cloruro de Sodio U.S.P.

En dextrosa al 5%	1.337 x 4.5 gr ÷ 1.000	= 6.02 Kgs
En dextrosa al 5%	48.802 x 9.0 gr ÷ 1.000	= 439.22 Kgs
En solución de Ringer	40.964 x 4.3 gr ÷ 1.000	= 176.15 Kgs
En lactato de sodio	404 x 5.0 gr ÷ 1.000	= 20.20 Kgs
En solución de Hartman	34.650 x 3.005 ÷ 1.000	= 104.12 Kgs
En suero fisiológico	8.087 x 45.0 ÷ 1.000	= 363.92 Kgs
		1.109.63 Kgs

Cloruro de Potasio U.S.P.

En solución de Ringer	40.964 x 0.15 gr ÷ 1.000	= 6.14 Kgs
En solución de Hartman	34.950 x 0.15 gr ÷ 1.000	= 5.20 Kgs
		11.34 Kgs

Cloruro de Calcio U.S.P.

En solución de Ringer	40.964 x 0.165 gr ÷ 1.000	= 6.76 Kgs

6/ VADEMECUM PLM. Méximo, Edición 1982.

En solución de Hartman	34.650 x 0.10 gr ÷ 1.000	=	6.76 Kgs
			10.23 Kgs
Lactato de Sodio U.S.P.			
En solución de Hartman	34.650 x 1.55 gr ÷ 1.000	=	53.71 Kgs
En lactato de sodio	404 x 50 ÷ 1.000	=	20.20 Kgs
			73.91 Kgs
	T O T A L		7.159.96 Kgs

La programación de producción debe hacerse de tal manera que se pueda espaciar en forma mas o menos regular la entrega de cada producto a los consumidores. Debido a que estos reactivos químicos son de importación se recomienda tener en almacenamiento por lo menos para 4 meses de producción.

3.8. Requerimiento de Energía

Las necesidades de energía en sus diferentes formas para este proceso serán, energía calorífica para la operación de esterilización de productos y de equipos utilizando vapor y para calentamiento de agua algunos flujos de servicios y energía eléctrica para movimiento mecánico de motores para bombeo, agitación, acondicionamiento de aire, etc. y para iluminación de los sitios de trabajo.

Como fuente para abastecer las necesidades de energía calorífica se ha incorporado una caldera de vapor cuyas características ya fueron descritas y que operará con ACPM como combustible. Para abastecer las necesidades de energía eléctrica se utilizaría la red de distribución municipal. Debido a que en esta región existe constantemente interrupción en el suministro de fluido eléctrico, es necesario dejar abierta la posibilidad de adquirir una sub-estación eléctrica que vaya adecuándose a la expansión en la producción de la planta.

CAPITULO IV

INVERSIONES

Las inversiones totales necesarias para la puesta en marcha del proyecto tienen un costo de $45'551.419 de los cuales el 68.42% corresponde a inversiones fijas, el 22.76% a Inversiones Diferidas y el 8.82% a capital de trabajo. En detalle se presenta esta distribución en el Cuadro 13, y su programación se encuentra identificada en el Cuadro 15, Calendario de Inversiones.

4.1. Inversiones Fijas

Las inversiones fijas están representadas por los activos adquiridos durante la etapa de instalación y montaje, para ser utilizados durante la vida útil del proyecto. Las inversiones fijas están constituidas, así:

4.1.1. Terrenos y Adecuaciones

Para la instalación de la nueva fábrica y considerando la posibilidad de futuras ampliaciones, la planta se construirá en una área de 5.000 metros cuadrados, cuyo valor global es de $5'000.000 y se estima por concepto de adecuación y reparación de vías internas de la zona un

Cuadro 13

PLANTA PRODUCTORA DE DEXTROSAS Y SIMILARES. INVERSIONES (FIJAS Y DIFERIDAS EN EL PROYECTO. CIFRAS EXPRESADAS EN PESOS CORRIENTES DE 1983

DESCRIPCION	VALOR	PORCENTAJE PARTICIPACION EN EL TOTAL
INVERSIONES FIJAS	31'165.700	100
TERRENOS		
Globo de terreno localizado en Pasto zona La Carolina 5.000 m2 a $1.000	5'000.000	16.04
Adecuación del terreno y reparación de vias (valor estimado) 6% costo del terreno, construcciones e instalaciones	300.000	0.96
Construcción del edificio para la Planta 1.020.85 m2 $10.000 m2 (*)	10'208.500	32.76
Redes de tubería de vapor, agua filtrada, agua blanda, agua deionizada, para inyección y aire 120 m a $960 m.	115.200	0.37
Acometida eléctrica de fuerza y teléfono	300.000	0.96
MAQUINARIA Y EQUIPO		
Equipo y dotación en general (Anexo)	12'742.000	40.88
VEHICULOS		
Camión para reparto	2'500.000	8.03

Cuadro 13: CONTINUACION

DESCRIPCION	VALOR	PORCENTAJE PARTICIPACION EN EL TOTAL
INVERSIONES DIFERIDAS	10'369.405	100
Instalación y montaje de equipos 15% del costo de equipo y dotación	1'911.300	18.43
Puesta en marcha y organización 2.5% del costo de Equipo y dotación	318.550	3.07
Imprevistos 10% items anteriores	3'339.555	32.21
Intereses durante la construcción y el montaje (Cuadro24)	4'800.000	46.29

(*) PROA. Profesionales Asociales. Costo a ABril de 1983

FUENTE: Esta investigación.

valor de $300.000, estimativo razonable por corresponder al 6% del costo total del terreno.

4.1.2. Construcciones e Instalaciones

Las construcciones necesarias para el montaje de la planta productora, en lo que se respecta al cerramiento del terreno, área para producción, área para laboratorios de control de calidad, almacenamiento, área para el sector administrativo, etc. se ha estimado en un costo de $10'623.700 en el cual están incluido costos por redes de tubería de vapor, agua filtrada, agua blanda, agua deionizada, aguas para inyección y además la acometida eléctrica de fuerza, y teléfono.

4.1.3. Maquinaria, Equipo y Dotación en General

La planta productora de dextrosas y similares, funcionará con maquinaria y equipo nacional y extranjero y tiene un costo de $12'742.000 su discriminación se encuentra en el Anexo 3.

4.1.4. Vehículos

La planta productora de dextrosas necesita un camión de reparto, de una capacidad de 9 toneladas, para que cumpla con el programa de entrega de la producción en toda el área de influencia. Su costo ha

sido cotizado en la suma de $2'500.000, como se puede apreciar en el Cuadro 13.

4.2. Inversiones Diferidas

4.2.1. Instalación y Montaje del Equipo

Se calcula en un 15% del costo total de maquinaria y equipo, por concepto de instalación y montaje y su valor asciende a la suma de $1'911.300.

4.2.2. Puesta en Marcha y Organización

Los costos ocasionados por la prueba de la maquinaria y equipo hasta lograr un normal funcionamiento y los de organización de la planta, se estiman en 2.5% del costo de Equipo y Dotación; estimativo razonable y que asciende a la suma de $318.550.

4.2.3. Imprevistos

Los imprevistos se calculan en un 10% del total de las inversiones fijas y diferidas, excluyendo los intereses a pagar durante la construcción y el montaje, y su valor es de $3'339.555.

4.2.4. Intereses durante la Construcción y el Montaje

Los intereses durante la construcción y el montaje tienen un valor de $4'800.000 calculados en base a un préstamo bancario de $20'000.000 con intereses del 24% anual, según puede verse en el Cuadro 24, Tabla de Amortización e Intereses.

4.3. Capital de Trabajo

El capital de trabajo requerido para operar la planta productora de Dextrosas y similares en el primer año es de $4'016.314 en la forma mostrada en el Cuadro 14, y sus cálculos se hicieron teniendo en cuenta los siguientes criterios:

4.3.1. Inventario de Materia Prima

El capital de trabajo por este concepto, para el primer año es de $274.465 correspondientes a la importación de materia prima para cuatro meses de existencia, teniendo en cuenta los requerimientos para el primer año de operación.

4.3.2. Inventario de Productos Terminados

El inventario de productos terminados y en cuarentena para su despa-

Cuadro 14

PLANTA PRODUCTORA DE DEXTROSAS Y SIMILARES. PASTO. CAPITAL DE TRABAJO

CIFRAS EXPRESADAS EN PESOS CORRIENTES 1983

DESCRIPCION	VALOR	PORCENTAJE DE PARTICIPACION EN EL TOTAL
CAPITAL DE TRABAJO		100
Inventario de Materias Primas (para 4 meses de producción) primer año de operaciones)	274.465	6.81
Inventario de Productos Terminados en cuarentena y para despachos (1.5 meses producción con costo directo)	1'595.344	39.81
Inventario de empaques, frascos, cajas tapones, etc. (1.5 meses producción)	268.870	6.67
Inventario de Insumos, combustibles, repuestos (1.5 meses de producción)	157.496	3.91
Gastos Generales (agua y luz para 1 mes)	56.825	1.42
Imprevistos 15% items anteriores	352.950	8.80
Mano de Obras para dos meses	1'310.364	32.52
RESUMEN		
INVERSIONES FIJAS	31'165.700	68.42
INVERSIONES DIFERIDAS	10'369.405	22.76
CAPITAL DE TRABAJO	4'016.314	8.82
T O T A L	45'551.419	100

cho, se calcula teniendo en cuenta 1.5 meses de producción al costo (costo directo), su resultado indica que el valor por este concepto asciende a la suma de $1'595.344.

4.3.3. Inventario de Empaques

El capital de trabajo requerido para los empaques de los diferentes productos, que lo constituyen los frascos, cajas, tapones, etc., para un período de 1.5 meses, es del orden de los $268.870.

4.3.4. Inventario de Insumos

Se consideró un inventario para un mes de producción y sus componentes son los combustibles, repuestos y otros elementos. Su costo aproximado es de $157.496.

4.3.5. Gastos Generales

Los gastos generales estimados para un mes de funcionamiento de la planta ascienden a la suma de $56.825 conformados por servicio de agua, energía y teléfonos.

4.3.6. Imprevistos

Se considera conveniente estimar un 15% de los anteriores conceptos

que constituyen el capital de trabajo como gastos imprevistos, debido a las diferencias que se presenten en el transcurso del desarrollo normal de la producción y su valor es de $352.950.

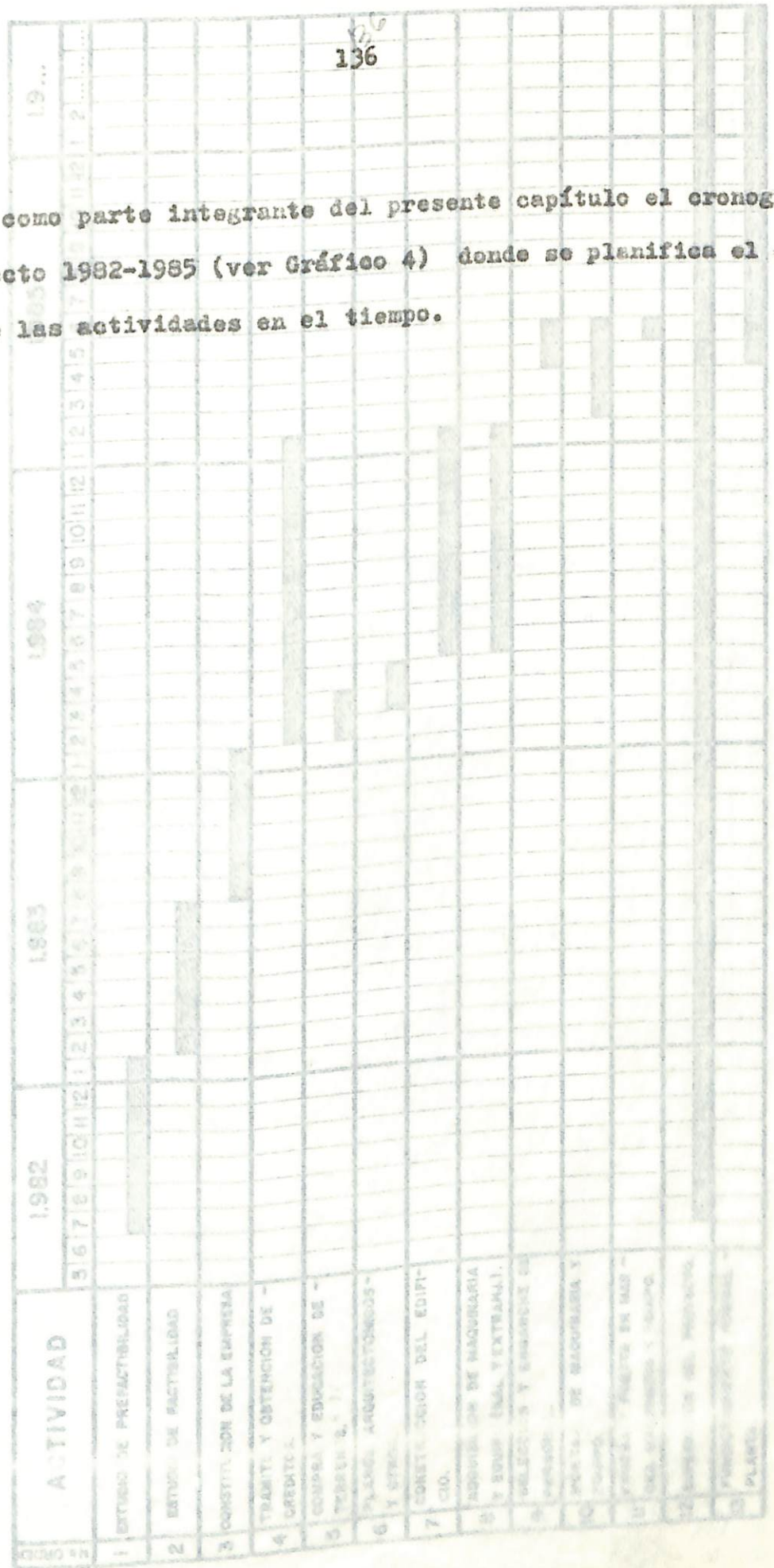
4.3.7. Mano de Obra

El valor de la mano de obra para dos meses de operación, asciende a la suma de $1'310.364. En este cálculo se incluyen salarios, subsidio de transporte y auxilio de alimentación y se toma como referencia el plan de salarios para 1983 vigentes en el Servicio de Salud de Nariño. (Ver Anexo 4)

4.4. Calendario de Inversiones

En el Cuadro 15 calendario de inversiones 1984-1985 expresado en pesos corrientes de 1983, se establece en forma trimestral las cantidades de dinero necesario en la inversión y se discrimina hacia que items debe orientarse el flujo de inversión, así se logra distribuir racionalmente las inversiones a medida que avanza el proyecto que asciende a la suma de $45'551.419, donde se incluyen inversiones fijas, diferidas y capital de trabajo, este último rubro considerado para el primer año de funcionamiento

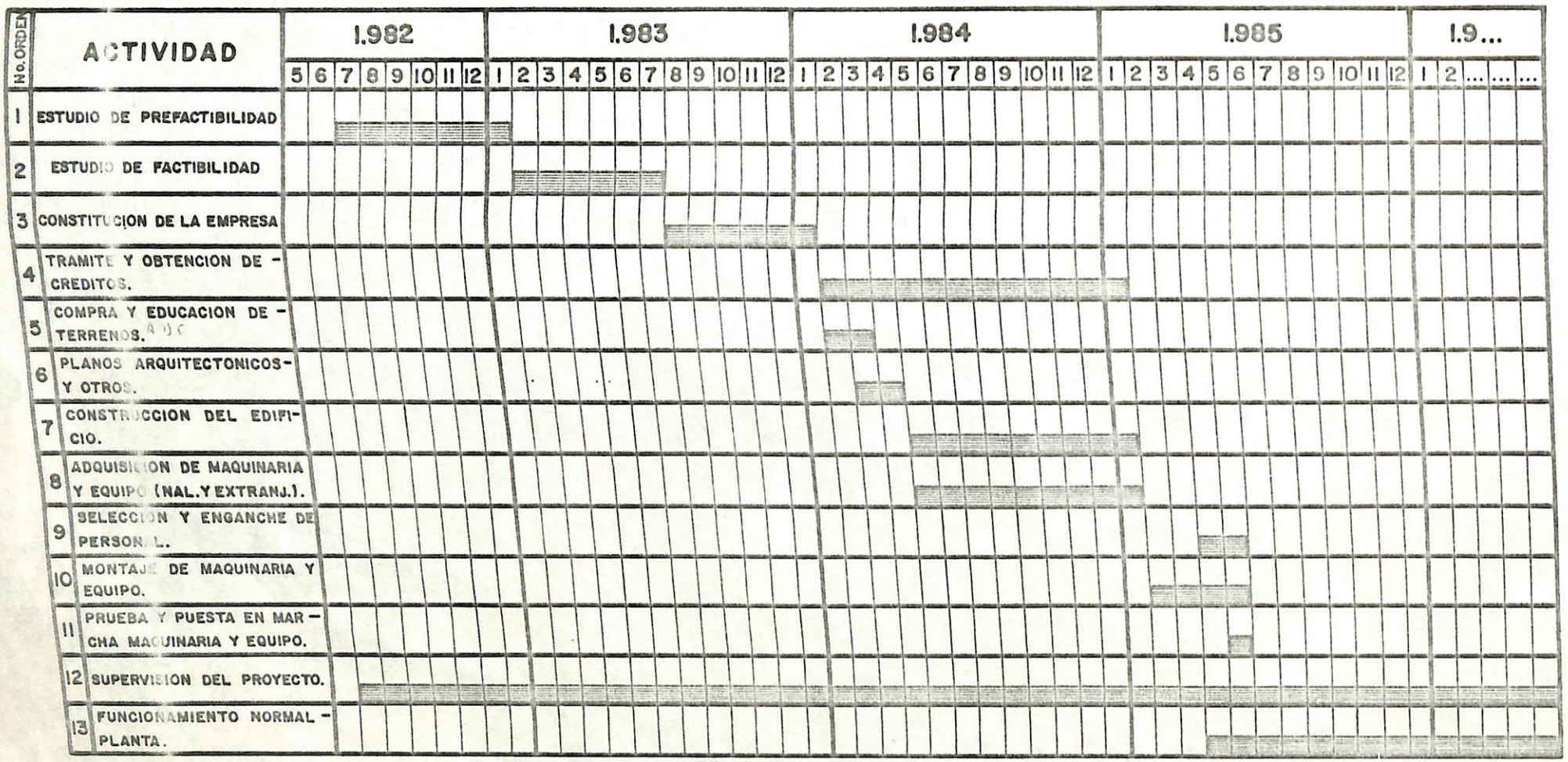
Se anexa como parte integrante del presente capítulo el cronograma del proyecto 1982-1985 (ver Gráfico 4) donde se planifica el desarrollo de las actividades en el tiempo.



Gráfica.: 4

PLANTA PRODUCTORA DE DEXTROSAS Y ELECTROLITOS
CRONOGRAMA DEL DESARROLLO DEL PROYECTO 1.982 —— 1.985

PASTO —— 1.983



FUENTE: Esta Investigación

Cuadro 15

PLANTA PRODUCTORA DE DEXTROSAS Y SIMILARES. PASTO 1983

CALENDARIO DE INVERSIONES 1984-1985. CIFRAS EXPRESADAS EN PESOS CORRIENTES

C O N C E P T O	1984 TRIMESTRES 2	3	4	1985 TRIMESTRES 1	2	3	4	TOTAL
NVERSIONES FIJAS Y DIFERIDAS								
ompra de terrenos	5'000.000							5'000.000
decuación de Terrenos	300.000							300.000
Construcción Edificio - redes								
ubería y acometida eléctrica		3'541.233	3'541.233	3'541.233				10'623.700
dquisición Maquinaria y Equipo		4'247.333	4'247.333	4'247.334				12'742.000
dquisición de vehículos						2'500.000		2'500.000
nstalación y montaje maquinaria					1'433.250	478.050		1'911.300
rganización y puesta en marcha						318.550		318.550
mprevistos	530.000	778.857	778.857	778.857	143.325	329.660		3'339.555
ntereses durante const. y montaje		960.000	960.000	960.000	960.000	960.000		4'800.000
UB TOTAL	5'830.000	9'527.423	9'527.423	9'527.424	2'536.575	4'586.260		41'535.105
APITAL DE TRABAJO								
nventario Materia Prima							274.465	274.465
nventario producto terminado							1'595.344	1'595.344
nventario de empaques							268.870	268.870
nventario Insumos y combustibles							157.496	157.496
astos Generales							56.825	56.825
mprevistos							352.950	352.950
ano de Obra							1'310.364	1'310.364
UB TOTAL							4'016.314	4'016.314
O T A L	5'830.000	9'527.423	9'527.423	9'527.424	2'536.575	4'586.260	4'016.314	45'551.419

FUENTE: Esta investigación.

CAPITULO V

PRESUPUESTO DE INGRESOS Y EGRESOS

5.1. Ingresos

Los ingresos del proyecto para el montaje de una planta productora de dextrosas en la ciudad de Pasto, con capacidad de abastecimiento para todo el Departamento de Nariño, están generados por la venta de la producción que se ha estimado para el primer año de operación en 311.040 frascos de 500 cc. por un valor total de $29'439.718 y para el décimo y último año de vida útil del proyecto $50'599.532, y una producción de 534.600 frascos.

En base al Cuadro 16 lista de precios al público, se obtiene el Cuadro 17 presupuesto anual de ingresos del proyecto, como resultado de multiplicar el precio del producto por la producción obtenida en el Cuadro 12 participación en la producción.

5.2. Egresos

Los egresos ocasionados por la operación de la planta productora de dextrosas, están clasificados de acuerdo a su origen en costos directos de producción, gastos generales de producción, gastos administra-

Cuadro 16

PLANTA PRODUCTORA DE SOLUCIONES ELECTROLITICAS. PASTO-NARIÑO

LISTA DE PRECIOS MAXIMOS AL PUBLICO, VIGENTE PARA 1983

No.	P R O D U C T O	PRECIO 1983
1	Dextrosa al 5% x 500 cc.	98.50
2	Dextrosa al 5% + Cloruro de Sodio al 0.45% Fco. 500 cc.	89.15
3	Dextrosa al 5% + Cloruro de Sodio al 0.9%	92.00
4	Dextrosa al 10% en A.D. x 500 cc.	98.50
5	Dextrosa al 10% en S.S. x 500 cc.	98.50
6	Lactato de Sodio x 500 cc	89.15
7	Solución Hartman x 500 cc.	90.90
8	Solución de Ringer x 500 cc.	89.40
9	Suero Fisiológico x 500 cc.	89.15
10	Agua Estéril x 500 cc.	72.00
	Precio Promedio Ponderado	$ 94.65

FUENTE: Esta Investigación.

Cuadro 17

PLANTA PRODUCTORA DE DEXTROSAS Y SIMILARES

PRESUPUESTO ANUAL DE INGRESOS

CIFRAS EXPRESADAS EN PESOS CORRIENTES DE 1983

Nº	NOMBRE DEL PRODUCTO	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994
01	Dextrosa al 5% en A.D. x 500 cc.	15'171.660	16'356.946	17'548.232	18'727.518	19'912.804	21'096.090	22'401.905	23'942.776	24'891.005	26'076.291
02	Dextrosa al 5% + Cloruro de sodio al 0.45% 500 cc.	119.194	128.551	137.866	147.181	156.496	165.812	174.059	188.169	195.621	204.936
03	Dextrosa al 5% + Cloruro de sodio al 0.9% x 500 cc.	4'489.784	4'840.566	5'191.321	5'542.097	5'892.863	6'243.628	6'629.471	7'085.466	7'366.073	7'716.844
04	Dextrosa al 10% A.D. 500 cc.	1'351.125	1'456.667	1'562.222	1'667.778	1'773.333	1'878.889	1'995.000	2'132.222	2'216.667	2'322.222
05	Dextrosa al 10% S.S. 500 cc.	324.755	350.128	375.500	400.872	426.243	451.615	479.524	512.507	532.804	558.176
06	Lactato de sodio x 500 cc.	36.017	38.864	41.680	44.497	47.313	50.129	53.227	56.888	59.141	61.957
07	Solución Hartman x 500 cc.	3'148.685	3'395.740	3'641.808	3'887.876	4'133.944	4'380.013	4'650.687	4'970.576	5'167.430	5'413.499
08	Solución Ringer x 500 cc	3'662.182	3'948.286	4'234.394	4'520.502	4'806.610	5'092.717	5'407.436	5'779.376	6'006.262	6'294.370
09	Suero Fisiológico	720.956	777.285	833.610	889.935	946.259	1'002.584	1'064.542	1'137.764	1'182.824	1'239.149
10	Agua estéril x 500 cc.	414.360	446.673	479.040	511.408	543.776	576.143	611.748	653.826	679.720	712.087
	TOTAL	29'439.718	31'739.706	34'039.685	36'339.664	38'639.642	40'939.621	43'469.598	46'459.570	48'299.552	50'599.531
PRODUCCION ANUAL TOTAL		311.040	335.340	359.640	383.940	408.240	432.540	459.270	490.860	510.300	534.600

FUENTE: Esta investigación.

Cuadro 18

PLANTA PRODUCTORA DE ELECTROLITOS. PRESUPUESTO ANUAL DE EGRESOS 1985-1994

CIFRAS EXPRESADAS EN PESOS CORRIENTES

CONCEPTO	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994
Porcentaje Capacidad Utilizada	58.18	62.73	67.27	71.82	76.36	80.91	85.91	91.82	95.45	100
Costos Directos de Producción y Materias Primas	823.395	887.723	952.051	1'016.379	1'080.436	1'145.035	1'215.796	1'299.422	1'350.681	1'415.142
INSUMOS										
Envases de Vidrio	1'455.960	1'569.707	1'683.454	1'797.201	1'910.948	2'024.695	2'149.817	2'297.688	2'388.631	2'502.613
Tapones, Agrafes, etc.	600.000	646.875	693.750	740.625	787.500	834.375	885.938	946.876	984.414	1'031.386
Empaques	95.000	102.422	109.844	117.266	124.688	132.110	140.274	149.927	156.182	163.619
Detergentes, Reactivos, etc.	350.000	377.344	404.688	432.032	459.376	486.720	516.798	552.345	575.409	602.809
Mano de Obra Directa	3'435.773	3'704.193	3'972.610	4'241.030	4'509.449	4'777.869	5'073.130	5'422.074	5636.480	5'905.456
Agua Potable	521.764	562.527	603.290	644.053	684.815	725.577	770.416	823.400	856.090	896.637
Energía Eléctrica 95%	149.697	161.392	173.087	184.782	196.477	208.172	221.037	236.241	246.106	257.825
Combustible A2C.P.M.	822.312	886.621	950.789	1'015.099	1'079.267	1'143.576	1'214.246	1'297.777	1'349.084	1'413.393
SUMAN (1)	8'253.901	8'898.804	9'543.563	10'188.467	10'832.956	11'478.129	12'187.452	13'025.758	13'543.077	14'188.880
GASTOS GENERALES DE PRODUCCION										
Mantenimiento y Reparación	300.000	300.000	300.000	300.000	300.000	300.000	300.000	300.000	300.000	300.000
Mano de Obra Indirecta	1'855.475	1'855.475	1'855.475	1'855.475	1'855.475	1'855.475	1'855.475	1'855.475	1'855.475	1'855.475
Seguros de Maquinaria y Equipo (1% de su valor)	152.420	152.420	152.420	152.420	152.420	152.420	152.420	152.420	152.420	152.420
Seguros Edificios (0.5% de su valor) 820.85 M2	43.918	43.918	43.918	43.918	43.918	43.918	43.918	43.918	43.918	43.918
Depreciaciones:										
Maquinaria y Equipo	1'218.200	1'218.200	1'218.200	1'218.200	1'218.200	1'218.200	1'218.200	1'218.200	1'218.200	1'218.200
Edificios	439.179	439.179	439.179	439.179	439.179	439.179	439.179	439.179	439.179	439.179
Vehículos	500.000	500.000	500.000	500.000	500.000	500.000	500.000	500.000	500.000	500.000
SUMAN (2)	4'509.192	4'509.192	4'509.192	4'509.192	4'509.192	4'009.192	4'009.192	4'009.192	4'009.192	4'009.192
GASTOS DE ADMINISTRACION										
Sueldos Personal Administ.	2'570.933	2'570.933	2'570.933	2'570.933	2'570.933	2'570.933	2'570.933	2'570.933	2'570.933	2'570.933
Agua	2.565	2.565	2.565	2.565	2.565	2.565	2.565	2.565	2.565	2.565
Energía 5%	7.878	7.878	7.878	7.878	7.878	7.878	7.878	7.878	7.878	7.878
Suministros Oficinas	60.000	60.000	60.000	60.000	60.000	60.000	60.000	60.000	60.000	60.000
Seguros Oficina (0.5% valor)	10.700	10.700	10.700	10.700	10.700	10.700	10.700	10.700	10.700	10.700
Depreciaciones Edificios	107.000	107.000	107.000	107.000	107.000	107.000	107.000	107.000	107.000	107.000
Transportes (combustibles)	284.000	284.000	284.000	284.000	284.000	284.000	284.000	284.000	284.000	284.000
Depreciaciones Maq.y Eq.	56.000	56.000	56.000	56.000	56.000	56.000	56.000	56.000	56.000	56.000
TOTAL COSTOS DE ADMON.	3'099.076	3'099.076	3'099.076	3'099.076	3'099.076	3'099.076	3'099.076	3'099.076	3'099.076	3'099.076
GASTOS FINANCIEROS	4'800.000	4'800.000	4'800.000	4'300.000	3'900.000	2'700.000	1'900.000	1'100.000	300.000	

Cuadro 18: CONTINUACION

CONCEPTO	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994
GASTOS DIFERIDOS										
AMORTIZACIONES										
Instalación y Montaje	191.130	191.130	191.130	191.130	191.130	191.130	191.130	191.130	191.130	191.130
Puesta en marcha	31.855	31.855	31.855	31.855	31.855	31.855	31.855	31.855	31.855	31.855
Imprevistos (Costos de Operación e Inversión fijas)	333.955	333.955	333.955	333.955	333.955	333.956	333.956	333.956	333.956	333.956
Intereses durante la construcción y el montaje	480.000	480.000	480.000	480.000	480.000	480.000	480.000	480.000	480.000	480.000
TOTAL GASTOS DIFERIDOS	1'036.940	1'036.940	1'036.940	1'036.940	1'036.940	1'036.941	1'036.941	1'036.941	1'036.941	1'036.941
TOTAL EGRESOS	21'699.109	22'344.012	22'988.771	23'133.675	22'978.164	22'323.338	22'232.661	22'270.967	21'988.286	22'334.089
PRODUCCION ANUAL TOTAL	311.040	335.340	359.640	383.940	408.240	432.540	459.270	490.860	510.300	534.600
COSTO UNITARIO TOTAL	69.76	66.63	63.92	60.25	56.28	51.60	48.40	45.37	43.09	41.78

FUENTE: Esta investigación.

tivos, gastos financieros y cargos diferidos.

El valor total de los egresos por los conceptos antes anotados para el primer año de operaciones de la planta será de $21'699.709 y para el décimo año de $22'334.089 según puede verse en el consolidado de Presupuesto de Egresos, Cuadro 18, calculado de acuerdo a las siguientes bases:

5.2.1. Costos Directos de Producción

Están constituidos por los costos incurridos en la compra de materia prima, insumos como envases de vidrio, tapones, agrafes y etiquetas, empaques, detergentes y reactivos, mano de obra directa, agua potable y energía, ACPM para funcionamiento de caldera y demás gastos generales de fabricación.

- Materia Prima

El costo por este concepto, corresponde a las necesidades de materia prima determinada en el capítulo III Ingeniría del Proyecto, Item 3.7. Requerimientos de Reactivos Químicos para el primer año de operaciones el requerimiento es de 7.160 kilogramos de reactivos calidad USP y su precio unitario de $115 para un costo total de $823.395 para los años siguientes, el incremento en el costo por este concepto corresponde al ensanchamiento de producción de la planta, de acuerdo a los datos presentados en el Cuadro 16, Tamaño del

proyecto con base en la demanda, y sus valores pueden verse consolidados en el Cuadro 18, Presupuesto de Egresos.

- Insumos:

-- Envases de Vidrio. Se ha estimado que para atender una producción 311.040 unidades, se requerirá de 220.000 envases nuevos que con su reutilización permitirán atender las necesidades. El costo de este elemento es de $6.618 millar, en producción nacional, según datos de 1983. El costo total por este concepto es de $1'455.960 para el primer año y para los años siguientes, el incremento corresponde al ensanche de la producción.

-- Tapones, Agrafes y Etiquetas. El costo total por este concepto se ha estimado en $600.000 para el primer año de operaciones y para los años siguientes su valor corresponde al incremento en la producción.

-- Empaques. Por este concepto se propone hacer reutilización de las cajas de empaque de las botellas vacías nuevas, a lo cual se adicionarían 3.800 cajas a un costo de $25 cada caja para un total de $95.000. Cada caja con capacidad para 25 botellas de producto.

-- Elementos Varios de Consumo. En este concepto se incluirán detergentes, reactivos para desinfecciones y lavados, elementos

de aseo, etc. y se estima un costo total de $350.000 para iniciar operaciones, estimación que dependerá en lo futuro de la producción.

- Mano de Obra Directa

Corresponde al personal involucrado directamente con la producción representando un costo anual de $3'435.773 incluidas prestaciones sociales. Por este concepto se incluye al personal de producción, detallados en Anexo 4.

- Agua Potable

El consumo anual será de 61.025 m^3 (248.011 galones) en el proceso de producción de soluciones y 300 m^3 (1.019 galones) adicionales para uso de oficinas e instalaciones sanitarias, con un costo de $8.55 cada metro cúbico, a 1983.

- Energía Eléctrica

Se ha estimado un consumo anual por este concepto de 70.980 Kw.H con un valor unitario de $2.22 según tarifas de 1983, el cual se distribuye en operaciones de producción de planta y demás actividades de orden administrativo. El costo total para iniciar operaciones es de $157.575, distribuidos en 95% para el proceso de producción y el 5% restante en actividades de orden administrativo, cada valor para los años siguientes está expresado en el Cuadro

sobre Presupuesto de Egresos.

- Combustibles.

En las actividades de operación de la caldera, cuyo funcionamiento es a base de ACPM, se estima un consumo de 11.664 galones para el primer año, con un precio unitario de $10.50 a 1983, para un costo total por este concepto de $822.312, los años siguientes muestran un crecimiento en este costo que corresponde al incremento en la producción.

- Gastos Generales de Producción

-- Mantenimiento y Reparaciones. Se ha estimado un costo por concepto de mantenimiento y reparaciones de maquinaria y equipo equivalente a $300.000 anuales.

-- Mano de Obra Indirecta. En este item se calcula el costo de la mano de obra indirecta constituida por el personal de control de calidad y Servicios Generales que tiene un costo anual incluidas prestaciones sociales de $1'855.475. (Ver Anexo 4)

-- Seguros de Maquinaria y Equipo. El costo por este concepto se ha estimado en el 1% de su valor, que corresponde a la suma de $152.420.

-- Seguros de Construcciones. Por concepto de seguros de las edi-

ficaciones donde funcionará la nueva unidad industrial, se ha estimado el 0.5% del valor total de las mismas. Esta estimación se efectúa en igual forma para instalaciones de producción y oficinas, su valor corresponde a $54.618, valor que se distribuye entre gastos generales de producción $43.918 y $10.700 como gastos de administración.

-- Depreciaciones. El valor de las depreciaciones, se estima en base a la vida útil de cada activo utilizando el método lineal. El costo total por este concepto es de $2'320.379 para el primer año de operaciones y el detalle por cada componente (maquinaria y equipo 10 años, edificios 20 años, vehículos 5 años y muebles y enseres 10 años) se muestra en el Cuadro 18, Presupuesto Anual de Egresos. (Ver Cuadro 29)

- Gastos de Administración

-- Sueldos Personal Administrativo. Corresponden a los sueldos, incluyendo prestaciones sociales del personal de almacenes, de oficinas y de dirección de la industria. El costo anual de este rubro es de $2'570.933, tal como puede verse en el Anexo 4, Requerimientos de Personal.

-- Agua y Energía. El costo por el primer concepto es de $2.565 y de energía $7.878, equivalente al 5% del gasto total.

-- Suministros Oficinas. Por concepto de papelería y útiles de oficina se estima un gasto anual de $60.000.

-- Combustibles para Vehículos. Se estima un consumo diario de 16.6 galones a un costo en 1983 de $70.50 galón por 243 dias laborales y se obtiene que el consumo anual es de $284.000.

- Gastos Financieros

Los intereses del 24% anual a pagar por el préstamo de $20'000.000 a largo plazo corresponde a los calculados en el Cuadro 24 y que para el primer año de vida útil del proyecto es de $4'800.000.

- Gastos Diferidos

En este rubro se consideran las amortizaciones durante los diez años de vida útil del proyecto de los gastos ocasionados por concepto de adecuación de terrenos, instalación de las redes de tubería y vapor, acometida eléctrica, instalación y montaje, puesta en marcha, imprevistos, que para cada período representa un costo de $1'036.940.

5.3. Punto de Nivelación

El punto de nivelación está definido como el porcentaje de la capacidad de operación de la fábrica en el cual los ingresos totales igualan a los costos totales, se ha calculado para el 100% de producción y gastos, utilizando para ello la siguiente fórmula:

$$P.N. = \frac{C.F.}{I.T. - C.V.} \times 100$$

Donde:

P.N. = Punto de Nivelación

C.F. = Costos Fijos

C.V. = Costos Variables

I.T. Ingresos Totales

Los costos para este cálculo se clasificaron en fijos y variables en atención a su comportamiento con la producción y su resultado puede apreciarse en el Cuadro 19.

El punto de nivelación para el proceso de producción de electrolitos se obtiene en el 36.92% de operación de la planta, en el cual los ingresos son $18'684.677.30 que se obtienen aplicándoles a los ingresos totales el porcentaje obtenido, así mismo a los costos variables mas los costos fijos que se consideran permanentes a lo largo de la vida útil del proyecto. (Ver Cuadro 20 y Gráfico 5)

Cuadro 19

PLANTA PRODUCTORA DE DEXTROSA Y SIMILARES. COSTOS FIJOS Y VARIABLES AL 100% DE PRODUCCION. CIFRAS EXPRESADAS EN PESOS CORRIENTES 1983

PASTO 1983

CONCEPTO	PARCIAL	TOTAL	%
I COSTOS FIJOS		13'445.209	48.65
Depreciaciones	2'320.379		
Sueldos de Administración	2'570.933		
Seguros de Maquinaria y Eq.	152.420		
Seguros de Construcciones	54.618		
Suministros Oficinas y Serv.	354.443		
Intereses sobre Préstamos	4'800.000		
Amortizac.Gastos Diferidos	1'036.941		
Mano de Obra Indirecta	1'855.475		
Mantenimiento y Reparaciones	300.000		
II COSTOS VARIABLES		14'188.880	51.35
Materias Primas	1'415.142		
Insumos	4'300.427		
Mano de Obra Directa	5'905.456		
Agua y Energía	1'154.462		
Combustibles	1'413.393		
TOTAL COSTOS FIJOS Y VARIABLES		27'634.089	100%

FUENTE: Esta Investigación.

Cuadro 20

PLANTA PRODUCTORA DE DEXTROSAS Y SIMILARES

CALCULO PUNTO DE NIVELACION AL 100%

DESCRIPCION	
Ingresos Totales al 100% producción (I.T.)	50'599.532
Costos Fijos (C.F.)	13'445.209
Costos Variables (C.V.)	14'188.880

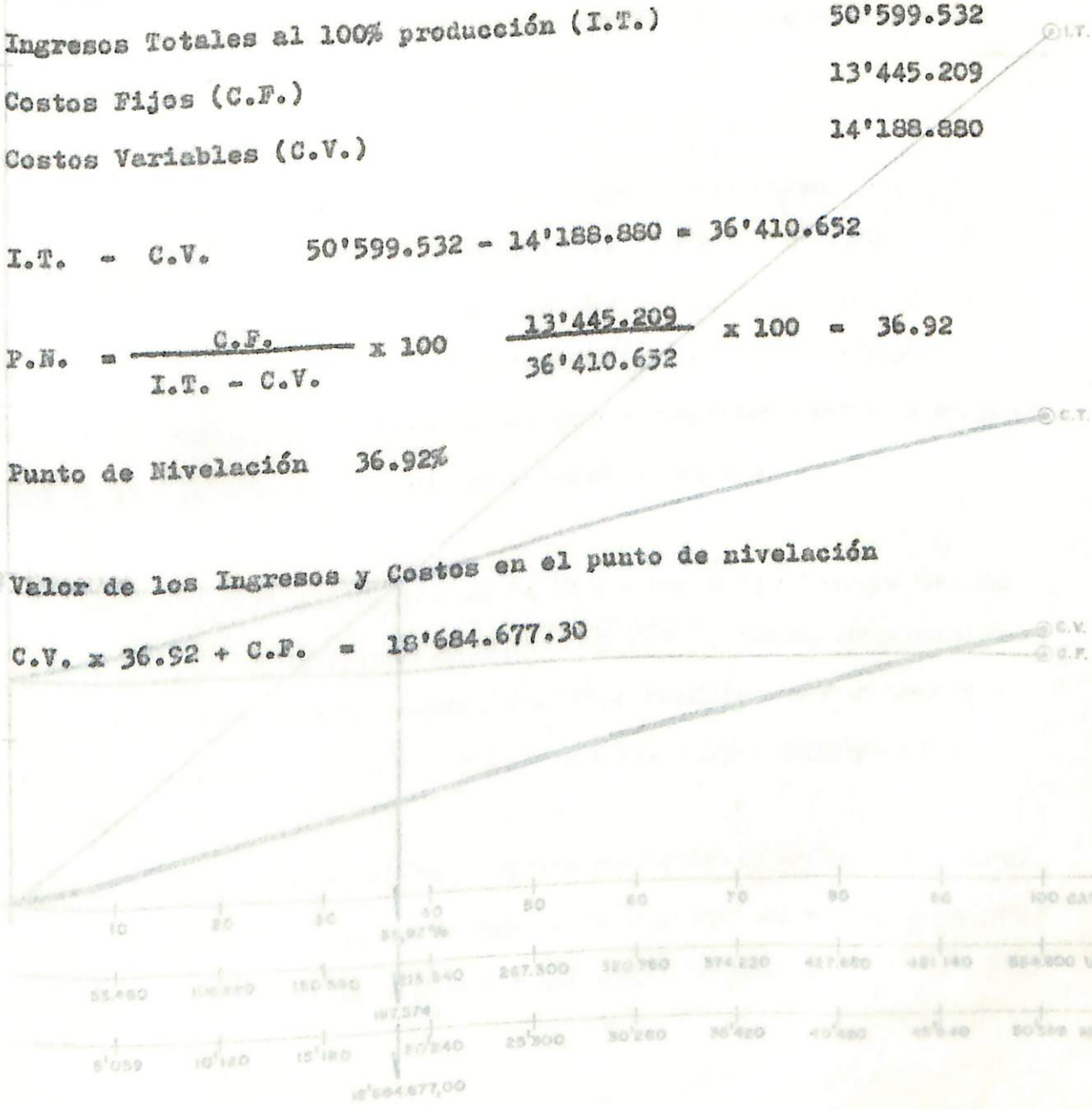
I.T. - C.V. 50'599.532 - 14'188.880 = 36'410.652

$$P.N. = \frac{C.F.}{I.T. - C.V.} \times 100 \qquad \frac{13'445.209}{36'410.652} \times 100 = 36.92$$

Punto de Nivelación 36.92%

Valor de los Ingresos y Costos en el punto de nivelación

C.V. x 36.92 + C.F. = 18'684.677.30

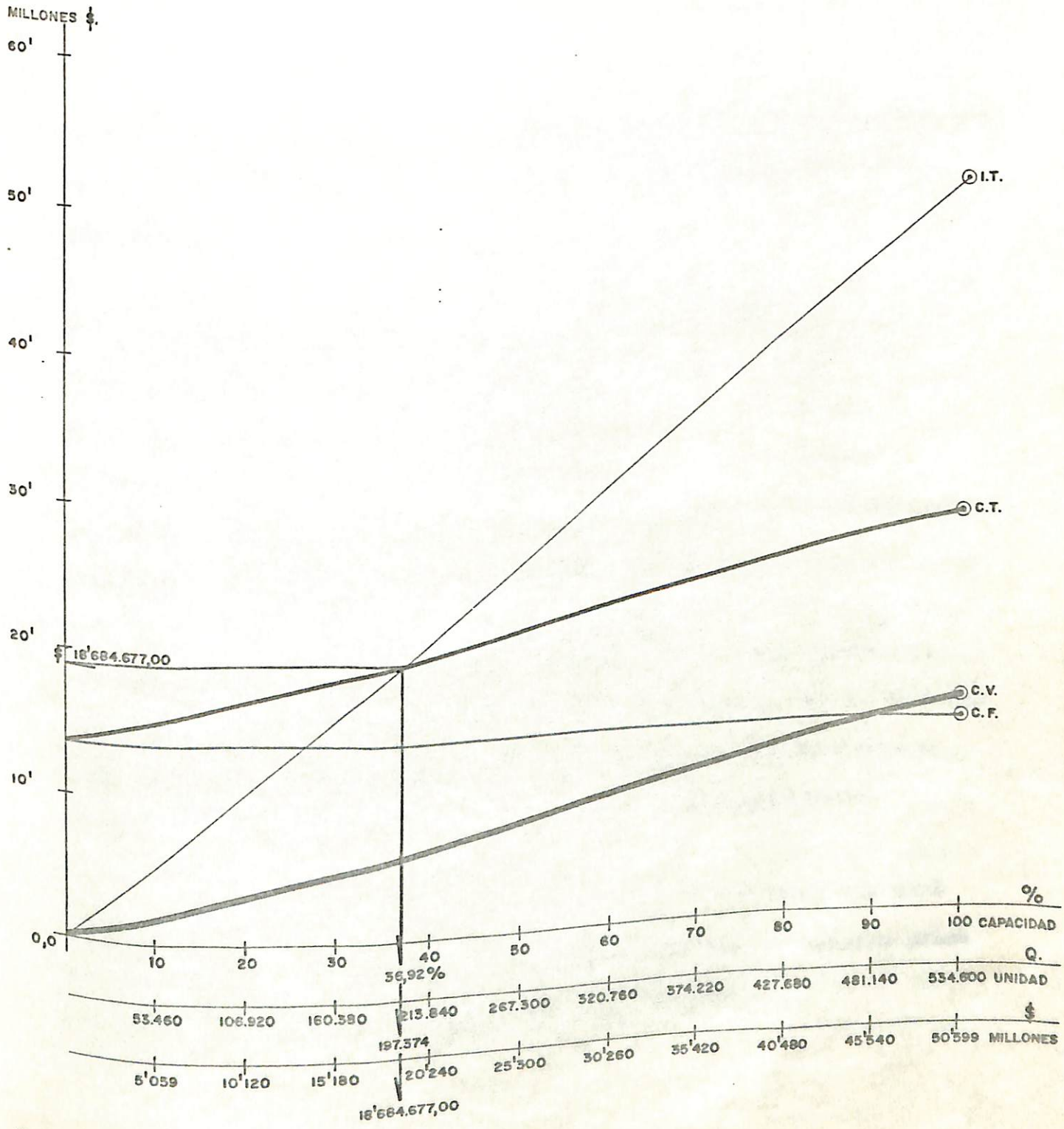


Fuente: Esta investigación.

Gráfica: 5

PLANTA PRODUCTORA DE DEXTROSAS Y ELECTROLITOS
PUNTO DE NIVELACION.

PASTO —— 1.983



FUENTE: Esta investigación.

CAPITULO VI

FINANCIAMIENTO

El Cuadro 21 presenta un resumen de la inversión y financiamiento para la vida útil del proyecto; la inversión total acumulada suma $45'551.419.

El financiamiento se discrimina de la siguiente forma:

Inversión Total	45'551.419	100%
Aporte de Socios	25'551.419	56.09
Crédito	20'000.000	43.91

El crédito financia el 43.9% de la inversión total, y cubre en parte los rubros de construcciones, maquinaria y equipo.

Las inversiones del proyecto serán financiadas con los aportes de los socios que constituyen la empresa y por entidades crediticias del orden nacional o internacional, en los rubros que tengan acceso a crédito de acuerdo a las exigencias de las líneas existentes.

Se plantean dos alternativas, siempre manteniendo la idea que será una empresa estatal, por lo tanto en la importación de materia prima se considera exenta de impuestos las adquisiciones.

Cuadro 21

PLANTA PRODUCTORA DE DEXTROSAS Y SIMILARES. ESTRUCTURA FINANCIERA 1983

CIFRAS EXPRESADAS EN PESOS CORRIENTES

FUENTE DE RECURSOS	MONTO ($)	% DE PARTICIPACION DE EL TOTAL
Prestamo Bancario	20'000.000	43.91
Aporte de los Socios	25'551.419	56.09
T O T A L	45'551.419	100%

FUENTE: Esta investigación.

Los costos laborales de personal se liquidarán teniendo en cuenta las disposiciones legales para empleados oficiales establecidas en los Decretos 1042 de 1978, 305 de 1981 y 110 de 1982.

6.1. Alternativa 1

Los socios que pueden constituir esta empresa puede ser entidad Tripartita Ltda. compuesta por:

El Servicio Seccional de Salud de Nariño

El Fondo Nacional Hospitalario o Minsalud

La Beneficencia de Nariño

La aportación de $25'551.419 que representa el 56.09% del total de la inversión del proyecto se puede dividir en aportaciones iguales que en términos de dinero significaría cuotas proporcionales de $8'517.140. Se definen estas tres entidades como socios por las siguientes razones:

- El Servicio Seccional es la máxima entidad rectora de la salud del Departamento y de él dependen legal y administrativamente 13 hospitales que son los principales consumidores de los productos materia de este proyecto.
- El Fondo Nacional Hospitalario o Minsalud es el organismo que apoya financieramente a los Servicios de Salud, para la construcción

de Hospitales y dotación, como se trata de un proyecto que tiene estrecha ligazón con el área médica, hospitalaria se pueden captar recursos por medio de esta entidad.

- La Beneficencia de Nariño (Lotería) su finalidad es aportar recursos para la prestación de servicios de salud a la comunidad, este proyecto reune todos los requisitos y tiene un objetivo, minimizar costos para el sector, existen experiencias al respecto, como es el caso de IFARBE (Instituto Farmacológico de la Beneficencia de Cundinamarca). Esta fábrica productora de drogas es de propiedad exclusiva de la Beneficencia de Cundinamarca.

6.2. Alternativa 2

Los socios lo pueden constituir una entidad Ltda. compuesta por el Servicio Seccional y los Hospitales, así:

- El Servicio Seccional de Salud de Nariño
- El Hospital Departamental de Pasto
- El Hospital Infantil Los Angeles de Pasto
- El Hospital San Pedro de Pasto
- El Hospital Eduardo Santos de La Unión
- El Hospital Clarita Santos, de Sandoná
- El Hospital San Carlos de San Pablo
- El Hospital El Buen Samaritano de La Cruz

- El Hospital San Vicente de Ipiales
- El Hospital San José de Túquerres
- El Hospital Lorencita Villegas de Santos, Samaniego
- El Hospital San Andrés de Tumaco
- El Hospital San Antonio de Barbacoas
- El Hospital Sagrado Corazón de Jesús, El Charco.

Su aporte a la sociedad sería en toma proporcional al presupuesto de funcionamiento aprobado para el año 1983. (Ver Cuadro 22)

6.3. Líneas de Financiación

Este proyecto puede financiarse a través de las siguientes líneas de crédito: Línea de Crédito Industrial del préstamo del Banco Internacional de Reconstrucción y Fomento -BIRF-; línea de Crédito del Fondo Financiero Industrial -FFI-; Línea de Crédito con el Banco Interamericano de Desarrollo -BID-, esto en cuanto se refiere a la búsqueda de recursos de crédito extremos por lo tanto deberá conseguirse en el país, y específicamente en Pasto un Banco local que haga las veces de intermediario.

El crédito interno se puede solicitar al Instituto de Fomento Industrial IFI, Corporación Financiera Popular, etc. El monto del préstamo solicitado de 20 millones de pesos a través de las anteriores lí-

Cuadro 22

PLANTA PRODUCTORA DE DEXTROSAS Y SIMILARES. APORTACION SOCIOS DE ACUERDO A PRESUPUESTO-1983

EN FORMA PROPORCIONAL (CIFRAS EXPRESADAS EN PESOS CORRIENTES)

N O M B R E	PRESUPUESTO	PORCENTAJE DEL TOTAL	VALOR
Servicio Seccional Sede	240'681.062	22.74	5'810.394
Hospital Departamental	219'622.729	20.76	5'304.474
" Infantil	51'261.436	4.85	1'239.244
" San Pedro	143.037.900	13.52	3'454.550
" Clarita Santos	25'055.193	2.38	608.124
" Eduardo Santos	42'791.333	4.04	1'032.278
" San Carlos	16'872.877	1.59	406.267
" El Buen Samaritano	17'475.677	1.65	421.598
" San Vicente	92'697.250	8.76	2'238.304
" San José	53'165.256	5.02	1'282.682
" Lorencita Villegas	24'785.650	2.34	597.903
" San Andrés	85'450.847	8.07	2'062.000
" San Antonio	29'211.254	2.76	705.219
" Sagrado Corazón	16'125.107	1.52	388.382
T O T A L	1.058'233.571	100	25'551.419

FUENTE; Esta Investigación.

neas será destinado al financiamiento de las inversiones fijas. Los recursos aportados por los socios serán destinados a cubrir parte de las inversiones fijas y a financiar el capital de trabajo de la nueva unidad productora.

Para los cálculos del presente proyecto se toma como referencia las líneas de crédito y las tasas de interés que maneja la Corporación Financiera Popular, y según se presenta en el Cuadro 23, el que se convierte en la base para trabajar la tabla de amortización de intereses, Cuadro 24.

6.4. Capacidad de Pago

Los resultados financieros obtenidos con la operación de la planta productora de dextrosas y similares, genera una adecuada capacidad de pago y endeudamiento, permitiendo atender eficientemente el servicio de la deuda compuesta por los intereses y la amortización, según puede verse en el Cuadro 25 Flujos de Caja Proyectados 1984-1994, donde se observa que quedan saldos disponibles desde el primer año de funcionamiento, lo cual deja ver una situación económica positiva. Así mismo, puede verse que la disponibilidad de saldos en Caja va creciendo a buen ritmo, pasando de $14'774.195 en el primer año de operaciones a $31'418.890 en el año de 1994.

Cuadro 23

PLAZOS E INTERESES DE FINANCIACION

	Plazo máximo año	Período gracia año	Intereses Anuales %
Compra de maquinaria	10	4	24
Construcciones	10	4	24
Capital de trabajo	5	1	22
Asistencia técnica	10	1	12

FUENTE: Corporación Financiera Popular, 1983.

Cuadro 24

PLANTA PRODUCTORA DE DEXTROSAS Y SIMILARES. TABLA DE AMORTIZACION DE INTERESES. 1984 - 1993

CIFRAS EXPRESADAS EN PESOS CORRIENTES

FUENTE DE PRESTAMO : CORPORACION FINANCIERA POPULAR
PLAZO TOTAL : 10 Años
PERIODO DE GRACIA : 4 Años
PERIODO DE AMORTIZ. : 6 Años
TASA DE INTERES SOBRE SALDOS : 24%

AÑOS	TRIMESTRE	DEUDA	AMORTIZACION ACUMULADA	INTERES TRIMESTRALES	INTERESES AÑO
1984	1o. a 4o.	20'000.000	15'833.332	250.000	4'800.000
1985	1o. a 4o.	20'000.000	16'666.666	200.000	4'800.000
1986	1o. a 4o.	20'000.000	17'499.999	150.000	4'800.000
1987	1o. a 4o.	20'000.000	18'333.332	100.000	4'800.000
	1o.	19'166.667	833.333	1'150.000	
1988	2o.	18'333.334	1'666.666	1'100.000	300.000
	3o.	17'500.001	2'499.999	1'050.000	
	4o.	16'666.668	3'333.332	1'000.000	4'300.000
1989	1o.	15'833.335	4'166.665	950.000	
	2o.	15'000.002	4'999.998	900.000	
	3o.	14'166.669	5'833.331	850.000	
	4o.	13'333.336	6'666.664	800.000	3'500.000

Cuadro 24: CONTINUACION

AÑOS	TRIMESTRE	DEUDA	AMORTIZACION ACUMULADA	INTERESES TRIMESTRALES	INTERESES AÑO
1990	1o.	12'500.003	7'499.997	750.000	
	2o.	11'666.667	8'333.333	700.000	
	3o.	10'833.334	9'166.666	650.000	
	4o.	10'000.001	9'999.999	600.000	2'700.000
1991	1o.	9'166.667	10'833.333	550.000	
	2o.	8'333.334	11'666.666	500.000	
	3o.	7'500.001	12'499.999	450.000	
	4o.	6'666.668	13'333.332	400.000	1'900.000
1992	1o.	5'833.334	14'166.666	350.000	
	2o.	5'000.000	14'999.999	300.000	
	3o.	4'166.668	15'833.332	250.000	
	4o.	3'333.334	16'666.666	200.000	1'100.000
1993	1o.	2'500.001	17'499.999	150.000	
	2o.	1'666.668	18'333.332	100.000	
	3o.	833.333	19'166.667	50.000	
	4o.		20'000.000	-	300.000

FUENTE: Esta investigación.

6.5. Estados Financieros Proforma

6.5.1. Estado de Pérdidas y Ganancias

Este importante estado financiero que indica las utilidades netas de cada ejercicio de la Planta Productora de Dextrosas y Similares, proyectado para el período 1985-1994, se trabaja bajo los supuestos de establecer los volúmenes de ventas, a las cuales se les ha deducido el 1% por concepto de devoluciones y todo el conjunto de costos de producción, manejando los conceptos de inventario inicial y final de mercancías, obteniendo en un primer paso las utilidades brutas de cada ejercicio, a la cual se deduce los gastos de operación, generales, administrativos y financieros, los dos primeros permanecen fijos durante todos los períodos y los financieros van decreciendo a medida que se amortizan la deuda, hasta que en el año último de vida útil del proyecto desaparecen por cancelación total del préstamo. Con lo anterior se obtiene la Utilidad Operacional a la que finalmente se restan los cargos diferidos que son fijos para todos los períodos obteniendo como último paso la utilidad neta del ejercicio, siendo para el año de 1985 de $9'041.556 y para el año 1994 de $27'877.213. Las utilidades obtenidas para los demás años, se pueden observar en el Cuadro 26. Se considera importante destacar que en el estudio financiero del proyecto no se contemplan reservas para pago de impuestos por tratarse de una empresa de propiedad del Gobierno, como

Cuadro 25

PLANTA PRODUCTORA DE DEXTROSAS Y SIMILARES

FLUJOS DE CAJA PROYECTADOS 1984-1994

CIFRAS EXPRESADAS EN PESOS CORRIENTES

DESCRIPCION	0 1984	1 1985	2 1986	3 1987	4 1988	5 1989	6 1990	7 1991	8 1992	9 1993	10 1994
INGRESOS											
Utilidad Bruta		22'486.764	22'648.270	24'280.215	25'912.566	27'544.781	29'176.861	30'984.555	33'131.274	34'368.018	36'024.422
Aportes de los socios	21'535.105	4'016.314	-	-	-	-	-	-	-	-	-
Préstamos	20'000.000	-	-	-	-	-	-	-	-	-	-
Cesantías consolidadas personal de producción		286.314	308.683	331.051	353.419	375.787	398.156	422.761	451.840	470.707	493.121
TOTAL INGRESOS	41'535.105	26'789.392	22'956.953	24'611.266	26'265.985	27'920.568	29'575.017	31'407.316	33'583.114	34'838.725	36'517.543
EGRESOS											
Inversiones Fijas	41'535.105	-	-	-	-	-	-	-	-	-	-
Incremento Activo Corriente		2'296.175	179.518	179.242	179.518	179.244	179.518	197.832	233.836	145.718	179.631
Gastos de Operación:											
Gastos Generales de Produc. (excluye depreciac.y cesantías)		2'197.190	2'197.190	2'197.190	2'197.190	2'197.190	2'197.190	2'197.190	2'197.190	2'197.190	2'197.190
Gastos Administrativos (excluye depreciaciones y cesantías)		2'721.832	2'721.832	2'721.832	2'721.832	2'721.832	2'721.832	2'721.832	2'721.832	2'721.832	2'721.832
Gastos Financieros		4'800.000	4'800.000	4'800.000	4'300.000	3'500.000	2'700.000	1'900.000	1'100.000	300.000	-
Amortización sobre préstamos	-	-	-	-	3'333.333	3'333.333	3'333.334	3'333.333	3'333.333	3'333.334	-
TOTAL DE EGRESOS	41'535.105	12'015.197	9'898.540	9'898.264	12'731.873	11'931.599	11'131.874	10'349.687	9'585.591	8'698.074	5'098.653
SALDO EN CAJA Y BANCOS	0	14'774.195	13'058.413	14'713.002	13'534.112	15'988.969	18'443.143	21'057.629	23'997.523	26'140.651	31'418.890

FUENTE: Esta investigación.

Cuadro 26

PLANTA PRODUCTORA DE MANITOSAS Y SIMILARES

ESTADO DE PERDIDAS Y GANANCIAS PROYECTADOS 1985 - 1994

CIFRAS EXPRESADAS EN PESOS CORRIENTES

DESCRIPCION	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994
Ventas Brutas	29'439.718	31'739.706	34'039.685	36'339.664	38'639.642	40'939.621	43'469.598	46'459.570	48'299.553	50'599.532
Menos devoluciones 1% ventas brutas	294.397	317.397	340.396	363.396	386.396	409.396	434.695	464.595	482.995	505.995
VENTAS NETAS	29'145.321	31'422.309	33'699.288	35'976.268	38'253.246	40'530.225	43'034.903	45'994.975	47'816.558	50'093.537
Inventario Inicial	0	1'595.344	1'720.109	1'844.599	1'969.364	2'093.855	2'218.620	2'355.724	2'517.781	2'617.318
Materias Primas	823.395	887.723	952.051	1'016.379	1'080.436	1'145.035	1'215.796	1'293.422	1'350.681	1'415.142
INSUMOS										
Envases de vidrio	1'455.960	1'569.707	1'683.454	1'797.201	1'910.948	2'024.695	2'149.817	2'297.688	2'393.631	2'507.613
Tapones, grapas, etc.	600.000	646.875	693.750	740.625	787.500	834.375	885.938	946.876	984.414	1'031.386
Empaques	95.000	102.422	109.844	117.266	124.688	132.110	140.274	149.927	156.182	163.619
Detergentes reactivos, etc.	350.000	377.344	404.688	432.032	459.376	486.720	516.798	552.345	575.409	602.809
Agua Potable	521.764	562.527	603.290	644.053	684.815	725.577	770.416	823.408	856.090	896.637
Energía Eléctrica	149.697	161.392	173.087	184.782	196.477	208.172	221.037	236.241	246.106	257.825
Combustible ACPM	822.312	886.621	950.789	1'015.000	1'079.267	1'143.576	1'214.246	1'297.777	1'349.084	1'413.393
Mano de obra directa	3'435.773	3'704.193	3'972.618	4'241.030	4'509.449	4'777.869	5'073.130	5'422.074	5'636.480	5'905.456
Menos Inventario final	1'595.344	1'720.109	1'844.599	1'969.364	2'093.855	2'218.620	2'355.724	2'517.781	2'617.318	2'742.083
UTILIDAD BRUTA	22'486.764	22'648.270	24'280.215	25'912.566	27'544.781	29'176.861	30'984.555	33'131.274	34'368.018	36'024.422
GASTOS DE OPERACION										
Costos Generales	4'509.192	4'509.192	4'509.192	4'509.192	4'509.192	4'009.192	4'009.192	4'009.192	4'009.192	4'009.192
Costos de Administración	3'099.076	3'099.076	3'099.076	3'099.076	3'099.076	3'099.076	3'099.076	3'099.076	3'099.076	3'099.076
Costos Financieros	4'800.000	4'800.000	4'800.000	4'300.000	3'500.000	2'700.000	1'900.000	1'100.000	300.000	0
UTILIDAD DE OPERACION	10'078.496	10'240.002	11'871.947	14'004.298	16'436.513	19'368.593	21'976.287	24'923.006	26'959.750	28'916.154
Menos Amortización Difer.	1'036.940	1'036.940	1'036.940	1'036.940	1'036.940	1'036.941	1'036.941	1'036.941	1'036.941	1'036.941
UTILIDAD DEL EJERCICIO	9'041.556	9'203.062	10'838.007	12'967.358	15'399.573	18'331.652	20'939.346	23'886.065	25'922.809	27'879.213
	9'041.556	18'244.618	29'079.625	42'046.983	57'446.556	75'778.208	96'717.554	120'603.619	146'526.428	174'405.641

FUENTE: Esta investigación.

Cuadro 27

PLANTA PRODUCTORA DE DEXTROSAS Y SIMILARES

BALANCE PROYECTADO 1985 - 1994

CIFRAS EXPRESADAS EN PESOS CORRIENTES

ACTIVO	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994
ACTIVO CORRIENTE										
Caja y Bancos	14'774.195	27'832.608	42'545.610	56'079.722	72'068.691	90'511.834	111'569.463	135'566.986	161'707.637	193'126.527
Inventarios:										
Materia Prima	274.465	295.908	317.350	338.793	360.236	381.678	405.265	433.141	451.227	477.714
Producto terminado Inv. final	1'595.344	1'720.109	1'844.599	1'969.364	2'093.855	2'218.620	2'355.724.	2'517.781	2'617.318	2'742.083
Empaques	268.870	289.875	310.881	331.886	352.892	373.898	397.004	424.311	442.028	463.077
Insumos	157.496	169.801	182.105	194.410	206.714	219.019	232.554	248.550	258.928	271.258
TOTAL ACTIVO CORRIENTE	17'070.370	30'308.301	45'200.545	58'914.175	75'082.388	93'705.049	114'960.010	139'190.769	165'477.138	197'080.659
ACTIVO FIJO										
Terrenos	5'000.000	5'000.000	5'000.000	5'000.000	5'000.000	5'000.000	5'000.000	5'000.000	5'000.000	5'000.000
Edificios	10'923.700	10'923.700	10'923.700	10'923.700	10'923.700	10'923.700	10'923.700	10'923.700	10'923.700	10'923.700
Maquinaria y Equipo	12'742.000	12'742.000	12'742.000	12'742.000	12'742.000	12'742.000	12'742.000	12'742.000	12'742.000	12'742.000
Vehículos	2'500.000	2'500.000	2'500.000	2'500.000	2'500.000	2'500.000	2'500.000	2'500.000	2'500.000	2'500.000
SUB TOTAL	31'165.700	31'165.700	31'165.700	31'165.700	31'165.700	31'165.700	31'165.700	31'165.700	31'165.700	31'165.700
Menos Depreciación acumulada	2'320.379	4'640.758	6'961.137	9'281.516	11'601.895	13'422.274	15'242.653	17'063.032	18'883.411	20'703.790
TOTAL ACTIVO FIJO	28'845.321	26'524.942	24'204.563	21'884.184	19'563.805	17'743.426	15'923.047	14'102.668	12'282.289	10'461.910
Activos Diferidos	10'369.405	10'369.405	10'369.405	10'369.405	10'369.405	10'369.405	10'369.405	10'369.405	10'369.405	10'369.405
Menos Amortización acumulada	1'036.940	2'073.880	3'110.820	4'147.760	5'184.700	6'221.640	7'258.580	8'295.520	9'332.460	10'369.405
TOTAL ACTIVO DIFERIDO	9'332.465	8'295.525	7'258.585	6'221.645	5'184.705	4'147.765	3'110.825	2'073.885	1'036.945	0
TOTAL ACTIVO	55'248.156	65'128.768	76'663.693	87'020.004	99'830.898	115'596.240	133'993.882	155'367.322	178'796.372	207'542.569

Cuadro 27: CONTINUACION

PASIVO	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994
PASIVO CORRIENTE										
Vencimiento corriente préstamo			3'333.333	3'333.333	3'333.334	3'333.333	3'333.333	3'333.334		0
TOTAL PASIVO CORRIENTE			3'333.333	3'333.333	3'333.334	3'333.333	3'333.333	3'333.334		
PASIVO A LARGO PLAZO										
Préstamo Bancario	20'000.000	20'000.000	16'666.667	13'333.334	10'000.000	6'666.667	3'333.334			
Cesantías Consolidadas	655.181	1'332.731	2'032.649	2'754.935	3'499.589	4'266.612	5'058.240	5'878.947	6'718.521	7'580.509
TOTAL PASIVO LARGO PLAZO	20'655.181	21'332.731	18'699.316	16'088.269	13'499.589	10'933.279	8'391.574	5'878.947	6'718.521	7'580.509
PATRIMONIO										
Capital suscrito y pagado	25'551.419	25'551.419	25'551.419	25'551.419	25'551.419	25'551.419	25'551.419	25'551.419	25'551.419	25'551.419
SUPERAVIT										
Utilidades del ejercicio	9'041.556	18'244.618	29'079.625	42'046.983	57'446.556	75'778.208	96'717.554	120'603.619	146'526.428	174'405.641
TOTAL PASIVO	55'248.156	65'128.768	76'663.693	87'020.004	99'830.898	115'596.239	133'993.880	155'367.319	178'796.368	207'537.569

FUENTE: Esta investigación.

Cuadro 28

PLANTA PRODUCTORA DE DEXTROSAS Y SIMILARES

CAPITAL DE TRABAJO 1985-1994

CIFRAS EXPRESADAS EN PESOS CORRIENTES

CAPITAL DE TRABAJO	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994
Inventario de Materias Primas (4 meses producción)	274.465	295.908	317.350	338.793	360.236	381.678	405.265	433.141	451.227	472.714
Inventario de productos terminados (1.5 meses producción Costos Directo)	1'595.344	1'720.109	1'844.599	1'969.364	2'093.855	2'218.620	2'355.724	2'517.781	2'617.318	2'742.083
Inventario de Empaques, frascos, cajas, etc. (1.5 meses)	268.870	289.875	310.881	331.886	352.892	373.898	397.004	424.311	442.028	463.077
Inventario de insumos (combustibles, repuestos) 1.5 meses	157.496	169.801	182.105	194.410	206.714	219.019	232.554	248.550	258.928	271.258
SUB-TOTAL	2'296.175	2'475.693	2'654.935	2'834.453	3'013.697	3'193.215	3'390.547	3'623.783	3'769.501	3'949.132
EFECTIVO										
Mano de obra (2 meses)	1'310.364	1'355.100	1'399.836	1'444.573	1'489.310	1'534.046	1'583.256	1'641.414	1'679.148	1'723.977
Gastos Generales (1 mes Agua-luz)	56.825	61.197	65.568	69.940	74.311	78.683	83.491	89.174	92.862	97.242
Imprevistos	352.950	380.534	408.075	435.659	463.201	490.785	521.106	556.944	579.354	606.956
SUB-TOTALA	1'720.139	1'796.831	1'873.479	1'950.172	2'026.822	2'103.514	2'187.853	2'287.532	2'351.364	2'428.175
TOTALES	4'016.314	4'272.524	4'528.414	4'784.625	5'040.519	5'296.729	5'578.400	5'911.315	6'120.865	6'377.307

FUENTE: Esta investigación.

Cuadro 28

PLANTA PRODUCTORA DE DEXTROSAS Y SIMILARES

CAPITAL DE TRABAJO 1985-1994

CIFRAS EXPRESADAS EN PESOS CORRIENTES

CAPITAL DE TRABAJO	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994
Inventario de Materias Primas (4 meses producción)	274.465	295.908	317.350	338.793	360.236	381.678	405.265	433.141	451.227	472.714
Inventario de productos terminados (1.5 meses producción Costos Directo)	1'595.344	1'720.109	1'844.599	1'969.364	2'093.855	2'218.620	2'355.724	2'517.781	2'617.318	2'742.085
Inventario de Empaques, frascos, cajas, etc. (1.5 meses)	268.870	289.875	310.881	331.886	352.892	373.898	397.004	424.311	442.028	463.077
Inventario de insumos (combustibles, repuestos) 1.5 meses	157.496	169.801	182.105	194.410	206.714	219.019	232.554	248.550	258.928	271.258
SUB-TOTAL	2'296.175	2'475.693	2'654.935	2'834.453	3'013.697	3'193.215	3'390.547	3'623.783	3'769.501	3'949.132
EFECTIVO										
Mano de obra (2 meses)	1'310.364	1'355.100	1'399.836	1'444.573	1'489.310	1'534.046	1'583.256	1'641.414	1'679.148	1'723.977
Gastos Generales (1 mes Agua-luz)	56.825	61.197	65.568	69.940	74.311	78.683	83.491	89.174	92.862	97.242
Imprevistos	352.950	380.534	408.075	435.659	463.201	490.785	521.106	556.944	579.354	606.956
SUB-TOTALA	1'720.139	1'796.831	1'873.479	1'950.172	2'026.822	2'103.514	2'187.853	2'287.532	2'351.364	2'428.175
TOTALES	4'016.314	4'272.524	4'528.414	4'784.625	5'040.519	5'296.729	5'578.400	5'911.315	6'120.865	6'377.307

FUENTE: Esta investigación.

Cuadro 29

PLANTA PRODUCTORA DE DEXTROSAS Y SIMILARES PASTO

DEPRECIACIONES 1985-1994. CIFRAS EXPRESADAS EN PESOS CORRIENTES

	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994
PRODUCCION										
Maquinaria y Equipo	1'218.200	1'218.200	1'218.200	1'218.200	1'218.200	1'218.200	1'218.200	1'218.200	1'218.200	1'218.200
Edificios	439.179	439.179	439.179	439.179	439.179	439.179	439.179	439.179	439.179	439.179
Vehículos	500.000	500.000	500.000	500.000	500.000					
SUB-TOTAL	2'157.379	2'157.379	2'157.379	2'157.379	2'157.379	1'657.379	1'657.379	1'657.379	1'657.379	1'657.379
ADMINISTRACION										
Edificios	107.000	107.000	107.000	107.000	107.000	107.000	107.000	107.000	107.000	107.000
Muebles y Enseres	56.000	56.000	56.000	56.000	56.000	56.000	56.000	56.000	56.000	56.000
SUB-TOTAL	163.000	163.000	163.000	163.000	163.000	163.000	163.000	163.000	163.000	163.000
TOTAL	2'320.379	2'320.379	2'320.379	2'320.379	2'320.379	1'820.379	1'820.379	1'820.379	1'820.379	1'820.379
TOTAL ACUMULADO	2'320.379	4'640.758	6'961.137	9'281.516	11'601.895	13'422.274	15'242.653	17'063.032	18'883.411	20'703.790

Cuadro 30

PLANTA PRODUCTORA DE DEXTROSAS Y SIMILARES. PASTO

CESANTIAS CONSOLIDADAS 1985-1994

CIFRAS EXPRESADAS EN PESOS CORRIENTES

CONCEPTO	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994
PRODUCCION										
Mano de Obra directa	286.314	308.683	331.051	353.419	375.787	398.156	422.761	451.840	470.707	493.121
Mano de Obra Indirecta	154.623	154.623	154.623	154.623	154.623	154.623	154.623	154.623	154.623	154.623
SUB-TOTAL	440.937	463.306	485.674	508.042	530.410	552.779	577.384	606.463	625.330	647.744
ADMINISTRACION										
Sueldos Personal Administrativo	214.244	214.244	214.244	214.244	214.244	214.244	214.244	214.244	214.244	214.244
T O T A L	655.181	677.550	699.918	722.286	744.654	767.023	791.628	820.707	839.574	861.988
TOTAL ACUMULADO	655.181	1'332.731	2'032.649	2'754.935	3'499.589	4'266.612	'058.240	5'878.947	6'718.521	7'580.509

FUENTE: Esta investigación.

se dejó dicho en anteriores párrafos.

6.5.2. Balances

Los balances proyectados muestran la situación financiera de la nueva empresa para los años 1985-1994 (ver Cuadro 27). Su estructura muestra los activos corrientes, fijos y diferidos, que para el primer año son de $55'248.156 y en el pasivo se muestra la manera como se financian los activos, ya sea con capital de la empresa o mediante obligaciones adquiridas. También el pasivo muestra las utilidades de cada ejercicio, las cuales se van acumulando con el propósito de dejar libertad a los socios o Junta Directiva para darles el destino que mejor convenga y orientados a ayudar a financiar los programas de salud o proyectar una ampliación de la factoría.

En la elaboración de los estados financieros proforma de que se ha hablado, se han utilizado los Flujos de Caja (Cuadro 25), Estados de Pérdidas y Ganancias (Cuadro 26), Capital de Trabajo (Cuadro 28), Cuadro de Depreciaciones (Cuadro 29) y Cesantías Consolidadas (Cuadro 30), Tabla de Amortización (Cuadro 24).

CAPITULO VII

ORGANIZACION

Para el desarrollo del presente proyecto se considera la creación de una Sociedad Ltda. constituida por dos alternativas propuestas en el capítulo anterior, una Sociedad Tripartita que la integran: El Servicio Seccional de Salud de Nariño, La Beneficencia de Nariño y El Fondo Nacional Hospitalario, la segunda alternativa conformada por el Servicio Seccional y los 13 Hospitales del Departamento.

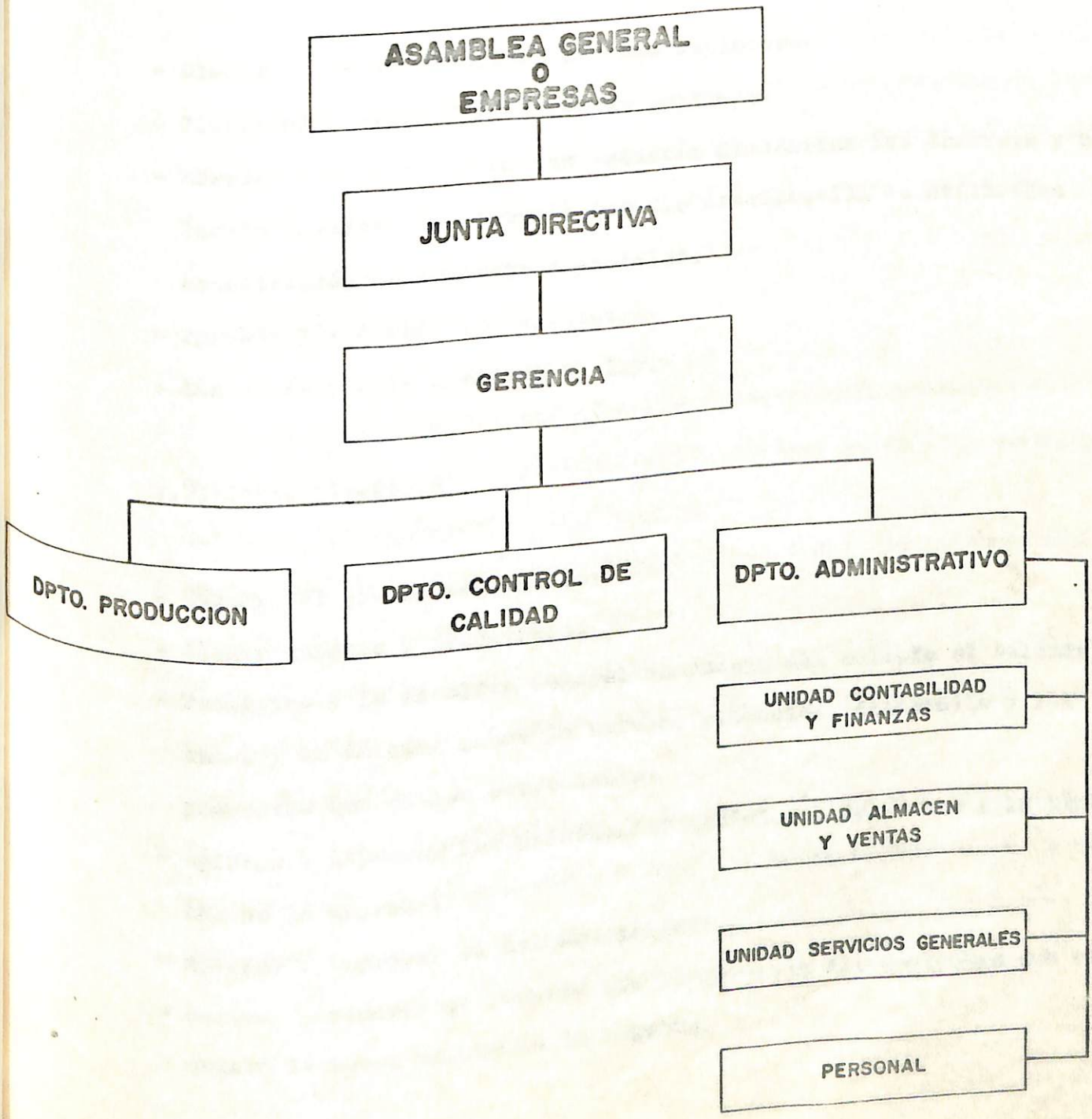
Se prevee para esta clase de empresa una organización tipo para entidades de Sociedades Ltdas. que permitirá a través del tiempo administrar técnicamente los recursos humanos y económicos con que cuenta la factoría.

La organización se desarrollará bajo los siguientes supuestos: Existirá una junta directiva que para el primer caso tendrá asiento en ella un representante con su respectivo suplente nombrado por la entidad participante de la sociedad tripartita. Para la segunda alternativa se establece una Asamblea General de Socios.

Los niveles de dependencia jerárquica se establecen en el Organigrama que se presenta en el Gráfico 6.

ORGANIGRAMA

PLANTA PRODUCTORA DE DEXTROSAS Y ELECTROLITOS



Las funciones que cumplirá cada uno de estos niveles serán:

7.1. Asamblea General de Socios

- Elegir la junta directiva con sus suplentes.
- Elegir el revisor fiscal con su suplente.
- Aprobar o desaprobar en sus sesiones ordinarias los informes y balances anuales, los proyectos sobre distribución de utilidades y constitución de reservas especiales.
- Aprobar y reformar los estatutos.
- Las demás que le confiera la ley.

7.2. Junta Directiva

- Expedir el propio reglamento.
- Elegir gerente y secretario.
- Presentar a la Asamblea General en asocio del Gerente el balance anual y un informe sobre la marcha, situación, desarrollo y los proyectos que estime conveniente.
- Aprobar e improbar las principales decisiones relativas a la marcha de la empresa.
- Aprobar e improbar el balance mensual.
- Nombrar y remover de acuerdo con la gerencia los empleados que requiera la buena marcha de la empresa.

- Reglamentar y modificar la política de manejo de la empresa.
- Fijar la remuneración del Gerente y los diferentes empleados de la empresa.
- Establecer y organizar de conformidad con los estatutos las diferentes dependencias de la empresa.
- Interpretar el sentido de los estatutos de la empresa cuando fuere necesario y dirimir las contradicciones que pueda presentarse entre ellos, dando cuenta a la Asamblea General o empresa nominadoras.

7.3. Revisor Fiscal

- Corresponde el examen, verificación y supervisión permanente de las operaciones, cuentas, existencia, documentos, garantía y demás que sean propios de la empresa.
- Tendrá derecho y facultad de inspeccionar todos los actos administrativos de la empresa.
- Tiene el deber de hacer que se cumplan los estatutos, los reglamentos y las resoluciones de la Asamblea General de socios y/o de la Junta Directiva.
- Asistir a todas las reuniones de la junta directiva y presentar un informe a la asamblea general o empresas sobre el ejercicio de sus funciones.

7.4. Gerencia

- LLevar a cabo la representación legal de la empresa.
- Ejecutar los acuerdos de la junta directiva.
- Celebrar los contratos y realizar las operaciones necesarias para el normal funcionamiento de la planta.
- Presentar a la junta directiva los planes que se requieran para desarrollar los programas de la factoría.
- Someter a consideración de la junta directiva los balances de la empresa.
- Presentar informes periódicos a la junta directiva sobre el estado y marcha de la empresa.
- Dirigir, coordinar y supervisar todas las actividades de la empresa en desarrollo de las políticas adoptadas.
- Proponer la creación, supervisión o fusión de cargos.
- Programar las actividades de la empresa en coordinación con los jefes de departamento.
- Las demás que le asigne la junta directiva.

7.5. Departamento de Producción

- Programar y ejecutar los programas de producción de la empresa.
- Rendir informes periódicos a la gerencia sobre la producción.
- Supervisar al personal de producción

- Las demás que le sean asignadas y estén acordes con la misión del departamento.

7.6. Departamento de Control de Calidad

- Ejercer control de calidad sobre los productos elaborados en la planta.
- Ejercer control de calidad sobre los inventarios de materia prima y producto terminado.

7.7. Departamento Administrativo

Este Departamento de infraestructura servirá de apoyo al desarrollo de la factoría, basado en los principios de organización: Planificación, Supervisión, Control. De él dependen las unidades de:

7.7.1. Unidad de Contabilidad y Finanzas

- Elaborar el presupuesto financiero de la empresa.
- Elaborar los registros contables y los estados financieros de la empresa.
- Elaborar los comprobantes de costos y gastos.
- Supervisar al personal de contabilidad.

- Rendir informes periódicos a la gerencia sobre los estados financieros de la empresa.

7.7.2. Unidad de Almacén y Ventas

Sus funciones serán:

- LLevar registros de entrada y salida de materias primas, kardex, etc.
- LLevar inventarios de productos terminados y almacenarlos debidamente.
- Coordinar la distribución de los productos elaborados por la empresa.
- Promover y adelantar campañas de promoción de ventas.
- Rendir informes periódicos a gerencia sobre el comportamiento de las ventas.
- Las demás que le sean asignadas.

7.7.3. Unidad de Servicios Generales

- Se encargará del transporte o sea distribución de productos de acuerdo a la organización mas adecuada, teniendo en cuenta la programación de abastecimiento a hospitales.
- El aseo deberá hacerse teniendo en cuenta las normas de control de calidad para zonas estériles y el resto de la factoría deberá permanecer en perfecto estado de limpieza.
- La celaduría se atenderá de acuerdo a turnos de trabajo y serán los

responsables de la planta.

7.7.4. Unidad de Personal

Esta unidad será la encargada del manejo del recurso humano.

- Velar por la armonía de las relaciones interpersonales y de empresa.
- Programar cursos de adiestramiento y capacitación, a fin de tener actualizado el personal.
- Elaborar la nómina mensual y registro de novedades.
- Liquidar Prestaciones Sociales.
- Las demás que le sean asignadas.

CAPITULO VIII

EVALUACION

En este capítulo se somete a los criterios de evaluación privada y social, el montaje de esta nueva factoría que se dedicará a la producción de Dextrosas y demás soluciones parenterales para todas las entidades de salud del Departamento.

8.1. Evaluación Privada

El rendimiento económico del proyecto se analizó mediante la Tasa Interna de Retorno TIR, Tasa Interna de Retorno Financiero para la empresa y para el empresario TIRF. Los resultados pueden observarse respectivamente en los Cuadros 31, 32 y 33, y son los siguientes:

8.1.1. Tasa Interna de Retorno TIR

La tasa interna de retorno del proyecto es del 32.93% según puede ver_
se en el Cuadro 31. Este cuadro ha sido actualizado a precios de
1983 y se considera una vida útil del proyecto de 10 años (1985-1994).
La TIR del 32.93% es muy ventajosa y hace que el proyecto en cuestión
sea bastante atractivo por encontrarse por encima del costo del capi-
tal que en este caso es del 24% anual

8.1.2. Tasa Interna de Retorno Financiero TIRF

- Para la Empresa:

El Cuadro 32 indica el procedimiento seguido para la obtención de la TIRF para la empresa y su resultado es del 46.50%. Se han calculado los flujos de inversiones fijas y aumentos en capital de trabajo como egresos necesarios para el funcionamiento de la factoría y el flujo operacional obtenido a partir de las rentas netas, disminuidas en todos los costos de producción directos e indirectos.

- Para el Empresario:

La TIRF para el empresario, se presenta en el Cuadro 33 y se obtiene a partir del cuadro anterior Flujo Neto para la Empresa. Aquí se vincula en forma separada la consecución de capital prestado y el costo de su reintegro.

La TIRF del 53.27% confirma las atractivas ventajas para la implantación de esta nueva fábrica.

8.2. Análisis de Sensibilidad

El objetivo de efectuar el análisis de sensibilidad es detectar las repercuciones en la rentabilidad del proyecto, considerando aumentos y disminuciones en el monto de las inversiones fijas y en las ventas netas.

El Cuadro 34 en el cual se consideran incrementos y disminuciones de 10% en las Inversiones Fijas, se ha elaborado en base al flujo neto para la empresa tomando el Cuadro 32, TIRF para la Empresa. Al aumentar las inversiones fijas de $41'535.105 a $45'688.616, la TIRF baja al 42.55% y mediante una disminución en las Inversiones Fijas del 10%, las que descienden a $37'381.595, la TIRF sube a 51.60%.

Al considerar aumentos y disminuciones en las ventas netas del orden del 10% (Cuadro 35), se tiene que la tasa interna de retorno financiero para la empresa, pasa del 40.94% cuando se presenta un incremento en las ventas netas al 30.14% cuando se presenta la baja.

Como puede observarse el proyecto ofrece niveles de sensibilidad bastante moderados tanto al estimular el costo de las inversiones fijas aumentándolas o disminuyéndolas, como al hacer variar los ingresos.

8.3. Evaluación Social

El impacto económico del proyecto se mide a través de la tasa interna de retorno económico TIRE, la cual da como resultado el 60.01%, en la forma como puede verse en el Cuadro 36.

Cuadro 31

- PLANTA PRODUCTORA DE DEXTROSAS Y SIMILARES

TASA INTERNA DE RETORNO DEL PRODUCTO—TIR

CIFRAS EXPRESADAS EN PESOS CORRIENTES, PASTO 1983

Concepto / Duración del Proyecto	0 1984	1 1985	2 1986	3 1987	4 1988	5 1989	6 1990	7 1991	8 1992	9 1993	10 1994
INGRESOS											
Ventas netas produc.	-	29'145.321	31'422.309	33'699.288	35'976.268	38'253.246	40'530.225	43'034.903	45'994.975	47'816.558	50'003.537
Vr. residual Inv. Fij.	-	-	-	-	-	-	-	-	-	-	10'461.910
Vr. residual Cap. Trab.	-	-	-	-	-	-	-	-	-	-	3'949.132
TOTAL DE INGRESOS	-	29'145.321	31'422.309	33'699.288	35'976.268	38'253.246	40'530.225	43'034.903	45'994.975	47'816.558	65'502.579
EGRESOS											
Inversiones fijas	41'535.105	-	-	-	-	-	-	-	-	-	-
Aumentos Capital de trabajo	-	2'296.175	179.518	179.242	179.518	179.244	179.518	197.332	233.236	145.718	179.631
Costo de Produc. - mv	-	6'658.557	8'774.039	9'419073	10'063.702	10'708.465	11'353.364	12'050.348	12'863.701	13'448.540	14'069.115
Gastos Generales (excluye deprec.)	-	2'351.813	2'351.813	2'351.813	2'351.813	2'351.813	2'351.813	2'351.813	2'351.813	2'351.813	2'351.813
Gastos de Administración - depreciac	-	2'936.076	2'936.076	2'936.076	2'936.076	2'936.076	2'936.076	2'936.076	2'936.076	2'936.076	2'936.076
Gastos Financieros	-	4'800.000	4'800.000	4'800.000	4'300.000	3'500.000	2'700.000	1'900.000	1'100.000	300.000	
Amortización Préstamos	-	-	-	-	3'333.333	3'333.333	3'333.334	3'333.333	3'333.333	3'333.334	
TOTAL DE EGRESOS	41'535.105	19'042.621	19'041.446	19'684.204	23'164.442	23'008.931	22'854.105	22'768.902	22'818.159	22'515.481	19'536.635
FLUJO NETO (FN)	(41'535.105)	10'102.700	12'380.863	14'015.084	12'811.826	15'244.315	17'676.120	20'266.001	23'176.816	25'301.077	45'967.944
Factores al 30% F 30		0.769231	0.591716	0.455166	0.350128	0.269329	0.207176	0.159366	0.122589	0.094300	0.072538
FN x F 30 + 3'986.183	(41'535.105)	7'771.310	7'325.955	6'379.190	4'485.779	4'105.736	3'662.068	3'229.712	2'841.223	2'385.892	3'334.423
Factores al 35% (F 35)		0.740741	0.548697	0.406442	0.30068	0.223014	0.165195	0.12236	0.090642	0.067142	0.049735
FN x F 35 - 2'819.363	(41'535.105)	7'483.484	6'793.342	5'696.319	3'857.231	3'399.695	2'920.007	2'479.890	2'100.793	1'698.765	2'286.216

TIR = 30 + 5 (3'986.183 / 6'805.546) = 32.93 %

FUENTE: Esta investigación.

Cuadro 32

PLANTA PRODUCTORA DE DEXTROSAS Y SIMILARES

TASA INTERNA DE RETORNO FINANCIERO TIRF PARA LA EMPRESA

CIFRAS EXPRESADAS EN PESOS CORRIENTES–PASTO 1983

Concepto / Duración del Proyecto	0 1984	1 1985	2 1986	3 1987	4 1988	5 1989	6 1990	7 1991	8 1992	9 1993	10 1994
INVERSIONES											
Fijas	(41'535.105)	-	-	-	-	-	-	-	-	-	-
Aumentos capital de trabajo		(2'296.175)	(179.518)	(179.242)	(179.518)	(179.244)	(179.518)	(197.332)	(233.236)	(145.718)	(179.631)
Valor residual capital de trabajo	-	-	-	-	-	-	-	-	-	-	3'949.132
Valor residual Activos fijos	-	-	-	-	-	-	-	-	-	-	10'461.910
FLUJO DE INVERSIONES	(41'535.105)	(2'296.175)	(179.518)	(179.242)	(179.518)	(179.244)	(179.518)	(197.332)	(233.236)	(145.718)	14'231.411)
FLUJO OPERACIONAL											
Ventas netas		29'145.321	31'422.309	33'699.288	35'976.268	38'253.246	40'530.225	43'034.903	45'994.975	47'816.558	50'093.537
-Costos de Produc.		6'658.557	8'774.039	9'419.073	10'063.703	10'708.465	11'353.364	12'050.348	12'863.701	13'448.540	14'069.115
-Gastos Generales		4'509.192	4'509.192	4'509.192	4'509.192	4'509.192	4'009.192	4'009.192	4'009.192	4'009.192	4'009.192
-Gastos de Admon.		3'099.076	3'099.076	3'099.076	3'099.076	3'099.076	3'099.076	3'099.076	3'099.076	3'099.076	3'099.076
Utilidad de Operación		14'878.496	15'040.002	16'671.947	18'304.298	19'936.522	22'068.593	23'876.287	26'023.006	27'259.750	28'916.154
Mas Depreciaciones		2'320.379	2'320.379	2'320.379	2'320.379	2'320.379	1'820.379	1'820.379	1'820.379	1'820.379	1'820.379
Amortización Diferidos		1'036.940	1'036.940	1'036.940	1'036.940	1'036.940	1'036.940	1'036.940	1'036.940	1'036.940	1'036.940
FLUJO OPERACIONAL		18'235.815	18'397.321	20'029.266	21'661.617	23'293.841	24'925.912	26'733.606	28'880.325	30'117.440	31'773.473
FLUJO NETO PARA LA EMPRESA FN	(41'535.105)	15'939.640	18'217.803	19'850.024	21'482.099	23'114.597	24'746.394	26'536.274	28'647.089	29(971.722	46'004.884
Factores al 45% (F 45)		0.689655	0.475624	0.328017	0.226218	0.156013	0.107595	0.0742034	0.051175	0.035293	0.024340
FN x F 45 + 1'374..763	(41'535.105)	10'992.855	8'664.829	6'511.140	4'859.646	3'606.171	2'662.588	1'969.083	1'466.008	1'057.791	1'119.757
Factores al 50% (F 50)		0.666666	0.444444	0.296296	0.197531	0.131687	0.087791	0.058528	0.039018	0.026012	0.017342
FN x F 50 - 3'222.305	(41'535.105)	10'626.426	8'096.801	5'881.487	4'243.376	3'043.897	2'172.521	1'553.104	1'117.764	779.630	797.794

T I R F para la empresa = 45 + 5 (1'374.763 / 4'597.068) = 46.50%

FUENTE: Esta investigación.

Cuadro 33

PLANTA PRODUCTORA DE DEXTROSAS Y SIMILARES

TASA INTERNA DE RETORNO FINANCIERO TIRF PARA EL EMPRESARIO

CIFRAS EXPRESADAS EN PESOS CORRIENTES. PASTO 1983

Concepto / Duración del Proyecto.	0 1984	1 1985	2 1986	3 1987	4 1988	5 1989	6 1990	7 1991	8 1992	9 1993	10 1994
FLUJO NETO EMPRESA	(41'535.105)	15'939.640	18'217.803	19'850.024	21'482.099	23'114.597	24'746.394	26'536.274	28'647.089	29'971.722	46'004.884
Intereses sobre préstamos	(41800.000)	(4'800.000)	(4'800.000)	(4'800.000)	(4'300.000)	(3'500.000)	(2'700.000)	(1'900.000)	(1'100.000)	(300.000)	
Amortización préstamos	-	-	-	-	(3'333.333)	(3'333.333)	(3'333.334)	(3'333.333)	(3'333.333)	(3'333.334)	
Préstamo	20'000.000										
FLUJO NETO PARA EL EMPRESARIO FN	26'335.105	11'139.640	13'417.803	15'050.024	13'848.766	16'281.264	18'713.060	21'302.941	24'213.756	26'338.388	46'004.884
Factores al 50% (F 50)		0.666666	0.444444	0.296296	0.197531	0.131687	0.087791	0.058528	0.039018	0.026012	0.017342
FN x F 50											
+ 1'710.990	26'335.105	7'426.419.	5'963.462	4'459.262	2'735.561	2'144.031	1'642.838	1'246.819	944.772	685.114	797.817
Factores al 60% (F 60)		0.625	0.390625	0.244141	0.152588	0.095367	0.059605	0.037253	0.023283	0.0145521	0.009095
FN x F 60											
- 3'516.886	26'335.105	6'962.275	5'241.329	3'674.322	2'113.154	1'552.702	1'115.385	793.596	563.770	383.274	418.412

TASA INTERNA DE RETORNO FINANCIERO TIRF PARA EL EMPRESARIO = 50 + 10 (1'710.990 / 5'227.876) = 53.27 %

FUENTE: Esta investigación.

Cuadro 34

PLANTA PRODUCTORA DE DEXTROSAS Y SIMILARES

ANALISIS DE SENSIBILIDAD CONSIDERANDO UN 10% DE AUMENTO Y DISMINUCION EN LAS INVERSIONES FIJAS

CIFRAS EXPRESADAS EN PESOS CORRIENTES. PASTO 1983

Concepto / Duración del Proyecto	0 1984	1 1985	2 1986	3 1987	4 1988	5 1989	6 1990	7 1991	8 1992	9 1993	10 1994
INVERSIONES FIJAS 10% AUMENTO											
Flujo neto empresa (FN)	(45'688.616)	15'939.640	18'217.803	19'850.024	21'482.099	23'114.597	24'746.394	26'536.274	28'647.089	29'971.722	46'004.884
Factores al 40% (F 40)		0.714286	0.510204	0.364431	0.260308	0.185934	0.132810	0.094865	0.067760	0.0484	0.034572
FN x F 40 + 2'901.544	(45'688.616)	11'385.451	9'294.797	7'233.974	5'591.967	4'297.799	3'286.576	2'517.351	1'941.137	1'450.639	1'590.463
Factores al 45% (F 45)		0.689655	0.475624	0.328017	0.226218	0.156013	0.107594	0.074203	0.051175	0.035293	0.024340
FN x F 45 - 2'778.762	(45'688.616)	10'992.855	8'664.829	6'511.140	4'859.647	3'606.171	2'662.573	1'969.083	1'466.008	1'057.791	1'119.757

T I R F = 40 + 5 (2'901.544 / 5'680.306) = 42.55 % (Aumento 10% en inversiones fijas)

INVERSIONES FIJAS 10% DISMINUCION											
Flujo neto empresa (FN)	(37'381.595)	15'939.640	18'217.803	19'850.024	21'482.099	23'114.597	24'746.394	26'536.274	28'647.089	29'971.722	46'004.884
Factores al 45% (F 45)		0.689655	0.475624	0.328017	0.226218	0.156013	0.107594	0.074203	0.051175	0.035293	0.024340
FN x F 45 + 5'528.259	(37'381.595)	10'992.855	8'654.829	6'511.140	4'859.647	3'606.171	2'662.573	1'969.083	1'466.008	1'057.791	1'119.757
Factores al 55% (F 55)		0.645161	0.416233	0.268537	0.173250	0.111774	0.072112	0.046524	0.030016	0.019365	0.012493
FN x F 55 - 2'845.125	(37'381.595)	10'283.639	7'582.852	5'330.475	3'721.773	2'583.615	1'784.521	1'234.577	859.858	580.399	574.761

T I R F = 45 + 10 (5'528-259 / 8'373.384) = 51.60 % (Disminución 10% en inversiones fijas)

FUENTE: Esta investigación.

Cuadro 35

PLANTA PRODUCTORA DE DEXTROSAS Y SIMILARES

ANALISIS DE SENBILIDAD CONSIDERANDO AUMENTOS Y DISMINUCIONES EN LAS VENTAS

CIFRAS EXPRESADAS EN PESOS CORRIENTES - PASTO 1983

Concepto / Duración del Proyecto	0 1984	1 1985	2 1986	3 1987	4 1988	5 1989	6 1990	7 1991	8 1992	9 1993	10 1994
INVERSIONES											
Fijas mas capital de trabajo	(41'535.105)	2'296.175	179.518	179.242	179.518	179.244	179.518	197.332	233.236	145.718	179.631
Vr. residual Activos fijos y capital de trabajo											14'411.042
FLUJO DE INVERSIONES	(41'535.105)	(2'296.175)	(179.518)	(179.242)	(179.518)	(179.244)	(179.518)	(197.332)	(233.236)	(145.718)	14'231.411
FLUJO OPERACIONAL CON AUMENTO EN VENTAS NETAS 10%											
Ventas Netas		32'059.853	34'564.540	37'069.217	39'573.895	42'078.571	44'583.248	47'338.393	50'594.473	52'598.214	55'102.891
-Costos de Producción		7'324.413	9'651.443	10'360.980	11'070.072	11'779.316	12'488.700	13'255.383	14'150.071	14'793.394	15'476.027
-Gastos Grales y de Administración		7'608.268	7'608.268	7'608.268	7'608.268	7'608.268	7'108.268	7'108.268	7'108.268	7'108.268	7'108.268
-Gastos Financieros		4'800.000	4'800.000	4'800.000	4'300.000	3'500.000	2'700.000	1'900.000	1'100.000	300.000	
-Amortizac.Préstamos					3'333.333	3'333.333	3'333.334	3'333.333	3'333.333	3'333.334	
Utilidad Operacional		12'327.172	12'504.829	14'299.969	13'262.222	15'857.654	18'952.946	21'741.409	24'902.801	27'063.218	32'518.596
Mas: Depreciaciones y diferidos		3'357.319	3'357.319	3'357.319	3'357.319	3'357.319	2'857.319	2'857.319	2'857.319	2'857.319	2'857.319
FLUJO OPERACIONAL		15'684.491	15'862.148	17'657.288	16'619.541	19'214.973	21'810.265	24'598.728	27'760.120	29'920.537	35'375.915
FLUJO NETO EMPRESA FN	(41'535.105)	13'388.315	15'682.630	17'478.046	16'440.023	19'035.729	21'630.747	24'401.396	27'526.885	29'774.819	49'607.326
Factores al 35% F 35		0.740741	0.548697	0.406442	0.301068	0.223014	0.165195	0.122367	0.090642	0.067142	0.049735
FNxF35 + 6'806.462	(41'535.105)	9'917.274	8'605.012	7'103.812	4'949.565	4'245.234	3'573.291	2'985.926	2'495.092	1'999.141	2'467.220
Factores al 45% F45		0.689655	0.475624	0328017	0.226218	0.156013	0.107595	0.074203	0.051175	0.035293	0.024340
FNxF45 - 4'642.592	(41'535.105)	9'206.542)	7'459.035	5'733.096	3'719.029	2'969.821	2'327.360	1'810.657	1'408.688	1'050.843	1'207.442

TASA INTERNA DE RETORNO FINANCIERO T I R F = 35 + 10 (6.806.462 / 11.449.054) = 40.94%

Cuadro 35: CONTINUACION

Concepto / Duración del Proyecto	0 1984	1 1985	2 1986	3 1987	4 1988	5 1989	6 1990	7 1991	8 1992	9 1993	10 1994
FLUJO OPERACIONAL CON DISMINUCION EN VENTAS NETAS DEL 10%											
Ventas netas		26'230.789	28'280.078	30'329.359	32'378.641	34'427.921	36'477.203	38'731.413	41'395.478	43'034.902	45'084.183
Menos: Costos de Producción 10%		5'992.701	7'896.635	8'477.166	9'057.332	9'637.619	10'218.028	10'848.313	11'577.331	12'103.686	12'662.204
Gastos Generales de Administración y financ.		12'408.268	12'408.268	12'408.268	11'908.268	11'108.268	9'808.268	9'008.268	8'208.268	7'408.268	7'108.268
Amortización Préstamo					3'333.333	3'333.333	3'333.334	3'333.333	3'333.333	3'333.334	
Utilidad Operacional		7'829.820	7'975.175	9'443.925	8'079.708	10'348.701	13'117.573	15'544.499	18'276.546	20'189.614	25'313.711
Mas: Depreciaciones y Diferidos		3'357.319	3'357.319	3'357.319	3'357.319	3'357.319	2'857.319	2'857.319	2'857.319	2'857.319	2'857.319
FLUJO OPERACIONAL		11'187.319	11'332.494	12'801.244	11'437.027	13'706.020	15'974.892	18'401.818	21'133.865	23'046.933	28'171.030
FLUJO NETO EMPRESA FN	(41'535.105	8'891.143	11'152.976	12'622.002	11'257.509	13'526.776	15'795.374	18'204.486	20'900.629	22'901.215	42'402.441
Factores al 35% F35		0.740741	0.548697	0.406442	0.301068	0.223014	0.165195	0.122367	0.090642	0.067142	0.049735
FN x F35 -6'915.481 (41'535.105)		6'586.034	6'119.604	5'130.112	3'389.276	3'016.660	2'609.317	2'227.628	1'894.475	1'537.633	2'108.885
Factores al 25% F25		0.8	0.64	0.512	0.14096	0.32768	0.262144	0.209715	0.167772	0.134218	0.107374
FN x F35 +7'313.341(41'535.105)		7'112.914	7'137.905	6'462.468	4'611.076	4'432.454	4'140.663	3'817.754	3'506.540	3'073.755	4'552-920

TASA INTERNA DE RETORNO FINANCIERO TIRF = 25 + 10 (7'313.341/14'228.822) = 30.14%

FUENTE: Esta Investigación.

Cuadro 36

PLANTA PRODUCTORA DE DEXTROSAS Y SIMILARES

TASA INTERNA DE RETORNO ECONOMICO

CIFRAS EXPRESADAS EN PESOS CORRIENTES. PASTO 1983

Concepto / Duración del Proyecto	0 1984	1 1985	2 1986	3 1987	4 1988	5 1989	6 1990	7 1991	8 1992	9 1993	10 1994
INVERSIONES											
Inversiones fijas y valor residual	31'165.700	-	-	-	-	-	-	-	-	-	10'461.910
Aumento Capital de trabajo		2'296.175	179.518	179.242	179.518	179.244	179.518	197.332	233.236	145.718	(179.631)
Valor residual capital de trabajo	-										3'949.132
FLUJO DE INVERSIONES	(31'165.700)	(2'296.175)	(179.518)	(179.242)	(179.518)	(179.244)	(179.518)	(197.332)	(233.236)	(145.718)	14'231.411
FLUJO OPERACIONAL		18'235.815	18'397.321	20'029.266	21'661.617	23'293.841	24'925.912	26'733.606	28'880.325	30'117.440	31'773.473
FLUJO NETO (FN)	(31'165.700)	15'939.640	18'217.803	19'850.024	21'482.099	23'114.597	24'746.394	26'536.274	28'647.089	29'971.722	46'004.884
Factores al 65 % FN x F 65		0.606060	0.367399	0.222612	0.134916	0.081767	0.049556	0.030034	0.018202	0.011032	0.006686
- 7'253.811	(31'165.700)	4'830.189	6'691.563	4'418.554	2'898.279	1'890.011	1'226.332	796.990	521.434	330.648	307.589
Factores al 60% FN x F 60		0.625	0.390625	0.244141	0.152588	0.095367	0.059605	0.037253	0.023283	0.014552	0.009095
+ 108.035	(31'165.700)	9'962.275	7'116.329	4'846.205	3'277.911	2'204.370	1'475.009	997.397	666.990	438.269	288.980

TASA INTERNA DE RETORNO ECONOMICO T I R E = 60 + 5 (108.035 / 1'361.846) = 60.01 %

FUENTE: Esta investigación.

CONCLUSIONES Y RECOMENDACIONES

En los capítulos y páginas precedentes, se han demostrado las posibilidades y conveniencias para el montaje y puesta en funcionamiento de una factoría dedicada a la producción de dextrosas y otros líquidos electrolíticos de uso hospitalario, capaz de abastecer toda la demanda observada en el Departamento de Nariño.

En este capítulo se puntualizan las conclusiones y recomendaciones finales obtenidas en el estudio realizado.

- Queda demostrado que existe un mercado para el consumo de dextrosas de una magnitud apreciable, compuesto por 13 hospitales en todo el Departamento de Nariño mas la Clínica del Seguro Social ubicada en Pasto, con un total de 702 camas instaladas y una ocupación del 67.78%
- Para el primer año de operaciones de la planta (1985) se espera una producción de 311.040 unidades de 500 cc que generará un ingreso de $29'439.718 y en el décimo año la producción será de 534.600 frascos y un ingreso de $50'599.532 a precios corrientes de 1983.
- Al demostrarse que la mejor localización de la factoría es Pasto, debe aprovecharse la situación geográfica de esta capital para proyectar en el futuro el mercado hasta la Intendencia del Putumayo y

sur de la República del Ecuador.

- Al operar con un sistema de comercialización directa entre productor y consumidor, se observa una serie de ventajas como reducción en costos de intermediación y comercialización y otros costos en que se incurre al otorgar sistemas o mecanismos de crédito.

- Este proyecto ha sido elaborado suponiendo que su montaje se llevará a efecto por iniciativa del Estado, a través del Servicio de Salud de Nariño que es una dependencia del Ministerio de Salud Pública. Esto hace que el proyecto goce de una serie de atractivos que inciden directamente en su rentabilidad, entre otros aspectos se destaca la facilidad en la consecución de materia prima importada, la cual se libera de todo gravamen por este concepto. Además de lo anterior, la nueva factoría se hallaría exenta de impuestos por las utilidades generadas en su operación. Estos y otros aspectos favorecen y posibilitan el montaje de la fábrica, ofreciendo índices altamente ventajosos como una TIR del 32.93%.

- Actualmente la prestación de servicios de salud se logra a un costo social muy elevado y el futuro en este aspecto se observa muy incierto, por la tendencia de los costos hacia el alza permanente y por las políticas económicas del país, encaminadas actualmente a reducir los gastos públicos, perjudicando las prioridades sociales

como mejorar el nivel de salud de la población. De allí que el montaje de una fábrica productora de medicamentos (dextrosas) que constituyen aproximadamente el 20% del costo de los servicios de salud hospitalarios y bajo los supuestos que se han fijado, le permitirán al Servicio de Salud de Nariño disponer de considerable utilidades económicas como se ha demostrado en los estados financieros proforma que hacen parte integrante de este estudio, que bajo un serio programa de ejecución se traducirán en beneficios para los ciudadanos.

Como beneficio económico social del proyecto, se puede decir que su inversión total que es de $45'551.419 genera un total de 28 nuevos empleos directos, a un costo promedio de $1'626.836 de capital por cada nuevo empleo. El valor agregado a la economía regional por concepto de remuneración al trabajo es de $7'862.181 para el primer año de operaciones de la fábrica, siendo en promedio $280.792 el valor agregado por cada empleo.

En lo que respecta a la participación de los 13 hospitales y el Servicio de Salud de Nariño como socios capitalistas de la factoría, esto puede lograrse mediante un adecuado plan de recuperación por venta de servicios a la comunidad, en tal forma que les permita aportar la cuota de capital que le corresponde a cada entidad, la cual se ha calculado en base a su capacidad presupuestal.

- Al calcularse el punto de equilibrio se puede establecer que éste se ubica en un 36.92% de capacidad de operación de la planta. Este porcentaje como puede verse se localiza muy por debajo de la producción en el primer año de actividades, la cual será de 311.040 frascos de 500 cc de producto, que utilizarán la planta a una capacidad del 58.18%.

- A pesar de que el presente estudio se realizó con la orientación de que su montaje sea emprendido por el estado y suponiendo que éste no considere prioritaria su ejecución, quedaría por complementarse la posibilidad de su realización por iniciativa privada, en cuyo caso es necesario realizar algunos ajustes contables, que afectarán levemente la rentabilidad del proyecto.

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A N E X O 1

Anexo 1

CALCULOS PARA PROYECCION DE LA DEMANDA

Para proyectar la demanda de Dextrosas y demás líquidos parenterales en el Departamento de Nariño, se toma como base el consumo histórico observado durante el periodo 1.977 a 1.981. Los resultados de esta observación se tabulan y con el objeto de buscar su tendencia, se calculan los valores estimados en cada una de las siguientes ecuaciones para posteriormente encontrar el menor valor de S (error típico) y definir que la ecuación a la que corresponda es la que en mejor forma describe el consumo observado.

1. Ecuación de Línea Recta:

$$Y = a + bx,$$

donde: Y = demanda (consumo),
a = consumo autónomo,
b = propensión al consumo,
x = periodicidad del tiempo.

2. Ecuación Parabólica:

$$Y = a + bx + cx^2$$

donde: Y, a, b, y x, corresponden a la misma definición de la ecuación anterior,
cx^2 = corresponde a la expresión cuadrática que defina a la ecuación parabólica.

3. Ecuación Exponencial:

$$Y = a + b^x$$

donde: Las variables se definen en igual forma que la ecuación de línea recta.

Anexo 1

CALCULOS PARA PROYECCION DE LA DEMANDA

GRUPO DEXTROSAS Y SOLUCIONES

1. Ecuación de Línea Recta

$Yc = a + bx$

AÑO	$\bar{x}$	y	xy	x^2	y^t	$(y-y^t)^2$	s
1977	-2	121.110	-242.220	4	118.663	5'987.809	
1978	-1	139.823	-139.823	1	141.764	3'767.481	
1979	0	158.865	0	0	164.865	36'000.000	
1980	1	196.010	196.010	1	187.966	64'705.936	
1981	2	208.519	417.038	4	211.067	6'492.304	
	0	824.327	231.005	10	824.325	116'953.530	6.244

$a = y/n$

$a = 824.327/5$

$a = 164.865$

$b = (xy)/ x^2$

$b = 231.005/10$

$b = 23.101$

$y_{-2} = 164.865 + 23.101 (-2) = 118.663$

$y_{-1} = 164.865 + 23.101 (-1) = 141.764$

$y_0 = 164.865 + 23.101 (0) = 164.865$

$y_1 = 164.865 + 23.101 (1) = 187.966$

$$y_2 = 164.865 + 23.101\ (2) = \frac{211.067}{824.325}$$

Cálculo del error típico

$$S = \sqrt{\frac{(y - y_t)^2}{v}} \qquad v = \text{No. de datos} - \text{No. de constantes}$$

2. Ecuación Parabólica

$$y_c = a + bx + cx^2$$

AÑO	x	y	x.y	x^2	x^2y	x^4	y^t	$(y-y^t)^2$	S
1977	-2	121.110	-242.220	4	484.440	16	119.477	2'666.689	
1978	-1	139.823	-139.823	1	139.823	1	141.357	3'363.556	
1979	0	158.865	0	0	0	0	164.051	26'894.596	
1980	1	196.010	196.010	1	196.010	1	187.559	71'419.401	
1981	2	208.519	417.038	4	834.076	16	211.881	11'303.044	
	0	824.327	231.005	10	1'654.349	34	824.325	115'647.286	7.604

$$a = (\ y - c\ x^2)/n = (824.327 - 407\ (10))\ /\ 5 = 164.051$$

$$b = \Sigma x.y/\ x^2 = 231.005/10 = 23.101$$

$$c = n\ \Sigma(x^2y) - \Sigma x^2\ y/n\ x^4 - (x^2)^2$$

$$c = 5(1.654.349) - 10(824.327)/5\ (34) - (10)^2$$

$$c = 8.271.745 - 8.243.270/170 = 100$$

Anexo 1: CONTINUACION

$c = 28.475/70$

$c = 407$

$y = a + bx + cx^2$

$y = 164.051 + 23.101x + 407x^2$

$y_{-2} = 164.051 + 23.101\ (-2) + 407\ (-2)^2 = 119.477$

$y_{-1} = 164.051 + 23.101\ (-1) + 407\ (-1)^2 = 141.357$

$y_{o} = 164.051 + 23.101\ (0) + 407\ (0)^2 = 164.051$

$y_{1} = 164.051 + 23.101\ (1) + 407\ (1)^2 = 187.559$

$y_{2} = 164.051 + 23.101\ (2) + 407\ (2)^2 = 211.881$

824.325

3. Ecuación Exponencial

$yc = a.bx$

AÑO	x	y	Log.y	x.Log.y	x^2	Log.yc	yc	$(y-yt)^2$	S
1977	-2	121.110	5.08318	-10.16636	4	5.084516	121.483	139.129	
1978	-1	139.823	5.14558	-5.14558	1	5.14638	140.081	66.564	
1979	0	158.865	5.20103	0	0	5.208244	161.525	7.085.600	
1980	1	196.010	5.29228	5.29228	1	5.270108	186.252	95.218.564	
1981	2	208.519	5.31915	10.63830	4	5.331972	214.768	39.050.001	
	0	824.327	26.0422	0.61864	10	26.04122	824.109	141.549.858	6.86 9

Anexo 1: CONTINUACION

$yc = a.b^x$

$\log. y_c = \log. A + (\log. b)x$

$\log. a = \log. y/n = 26.04122/5 = 5.208244$

$\log. b = (x) \log. y / x^2$

$\log. b = 0.61864/10 = 0.0611864$

$\log. y_c = 5.208244 + 0.061864\ x$

$\log. y_{-2} = 5.208244 + 0.061864\ (-2) = 5.084516$

$\log. y_{-1} = 5.208244 + 0.061864\ (-1) = 5.14638$

$\log. y_o = 5.208244 + 0.061864\ (0) = 5.208244$

$\log. y_1 = 5.208244 + 0.0611864\ (1) = 5.270108$

$\log. y_3 = 5.208244 + 0.061864\ (2) = 5.331972$

DEXTROSAS Y SOLUCIONES FCO. x 500 cc.

AÑO	CONSUMO OBSERVADO	ECUACION LINEA RECTA(y=a+bx)	ECUACION PARABOLICA ($y=a+bx+cx^2$)	ECUACION EXPONENCIAL ($y = a.b^x$)
1977	121.110	118.663	119.477	121.483
1978	139.823	141.764	141.357	140.081
1979	158.865	164.865	164.051	161.525
1980	196.010	187.966	187.559	186.252
1981	208.519	211.067	211.881	214.768
	824.327	824.325	824.325	824.109
	Error típico	6.244	7.604	6.869

Anexo 1: CONTINUACION

Proyección de la Demanda por Ecuación de Línea Recta (menor error típico)

10 años

1985 a 1995

Ecuación $y = a + bx$

$y = 164.865 + 23.101\ x$

Año	x	y
1985	6	303.471
1986	7	326.572
1987	8	349.673
1988	9	372.774
1989	10	395.875
1990	11	418.976
1991	12	442.077
1992	13	465.178
1993	14	488.279
1994	15	511.380

GRUPO DE BICARBONATOS

1. Ecuación de Línea Recta

$y = a + bx$

Anexo 1: CONTINUACION

AÑO	x	y	x.y	x^2	x^2y	x^4	yt	$(y-yt)^2$	S
1977	-2	20.809	-41.618	4	83.236	16	22.410	2.563.201	
1978	-1	29.396	-29.296	1	29.296	1	25.302	15.952.086	
1979	0	32.124	0	0	0	0	34.497	5.631.129	
1980	1	49.167	49.167	1	49.167	1	49.996	687.241	
1981	2	72.610	145.220	4	290.440	16	71.800	656.100	
	0	204.006	123.473	10	452.139	34	204.005	25.489.707	3.570

$yt = a + bx + cx^2$

$a = (y - c\ x^2)/n = 204.006 - 3.152\ (10)\ /5 = 34.497$

$b = x.y/\ x^2 = 123.473/10 = 12.347.3$

$c = n\ x^2.y - x^2.\ y/n\ x^4 - (x^2)^2$

$c = 5(452.139) - 10(204.006)\ /5\ (34) - (10)^2$

$c = 2.260.695 - 2.040.060\ /170 - 100$

$c = 220.635/70 = 3.152$

$yt = a + bx + cx^2$

$yt = 34.497 + 12.347x + 3.152\ x^2$

$y_{-2} = 34.497 + 12.347\ (-2) + 3.152\ (-2)^2 = 22.410$

$y_{-1} = 34.497 + 12.347\ (-1) + 3.152\ (-1) = 25.302$

$y_0 = 34.497 + 12.347\ (0) + 3.152\ (0) = 34.497$

$y_1 = 34.497 + 12.347\ (1) + 3.152\ (1) = 49.996$

Anexo 1: CONTINUACION

$$y_2 = 34.497 + 12.347\ (2) + 3.152\ (2) = 71.800$$
$$= 204.005$$

3. Ecuación Exponencial

$yc = a.b^x$

AÑO	x	y	Log.y	x Log.y	x^2	Log.yc	yc	$(y - yt)^2$	S
1977	-2	20.809	4.31825	-8.6365	4	4.30682	20.268	292.681	
1978	-1	29.296	4.46681	-4.46681	1	4.43786	27.407	3.568.321	
1979	0	32.124	4.50683	0	0	4.56891	37.061	24.373.969	
1980	1	49.167	4.69167	4.69167	1	4.699958	50.114	896.809	
1981	2	72.610	4.86100	9.72200	4	4.831004	67.765	23.474.025	
	0	204.006	22.84456	1.31046	10	22.84456	202.615	52.605.805	4.188

$yc = a.b^x$

$\log.yc = \log.a + (\log.b)x$

$\log.a = \log.y/n = 22.84456/5 = 4.568912$

$\log.b = x\log.y/x^2 = 1.31046/10 = 0.131046$

$\log.yc = 4.568912 + 0.131046\ x$

$\log.y_{-2} = 4.568912 + 0.131046\ (-2) = 4.30682$

$\log.y_{-1} = 4.568912 + 0.131046\ (-1) = 4.437863$

$\log.y_o = 4.568912 + 0.131046\ (0) = 4.568912$

Anexo 1: CONTINUACION

$\log.y_1 = 4.568912 + 0.131046\ (1) = 4.609958$

$\log.y_2 = 4.568912 + 0.131046\ (2) = 4.831004$

BICARBONATOS FCO. x 10 cc.

AÑO	CONSUMO OBSERVADO	ECUACION LINEA RECTA (y=a+bx)	ECUACION PARABOLICA ($y=a+bx+cx^2$)	ECUACION EXPONENCIAL ($y = a.b^x$)
1977	20.809	16.107	22.410	20.268
1978	29.296	29.454	25.302	27.407
1979	32.124	40.801	34.497	37.061
1980	49.167	53.149	49.996	50.114
1981	72.610	65.496	71.800	67.765
	204.006	204.006	204.005	202.615
	Error típico	7.407	3.570	4.188

Proyección Ecuación Parabólica

$yt = a + bx + cx^2$

$y = 34.497 + 12.347\ x + 3.152\ x^2$

Año	x	y
1985	6	222.051
1986	7	275.374
1987	8	335.001
1988	9	400.932

Anexo 1: CONTINUACION

Año	x
1989	10
1990	11
1991	12
1992	13
1993	14
1994	15

GRUPO DE AGUA ESTERIL

1. Ecuación de Línea Recta

$y = a + bx$

AÑO	x	y	x.y	x^2	yt	$(y - yt)^2$	S
1977	-2	211.242	-422.484	4	175.722.8	1.261.613.568	
1978	-1	236.745	-236.745	1	293.379.3	3.207.443.936	
1979	0	425.775	0	0	411.035.8	217.244.017	
1980	1	527.040	527.040	1	528.692.3	2.730.095	
1981	2	654.377	1.308.754	4	646.348.8	64.451.995	
	0	2.055.179	1.176.565	10	2.055.179	4.753.483.610	39.806

$y = a + bx$

Anexo 1: CONTINUACION

$a = y/n = 2.055179/5 = 411.035.8$

$b = (x.y)/x^2 = 1.176.565/10 = 117.656.5$

$yt = 411.035.8 + 117.656.5\ x$

$y_{-2} = 411.035.8 + 117.656.5\ (-2) = 175.722.8$

$y_{-1} = 411.035.8 + 117.656.5\ (-1) = 293.379.3$

$y_0 = 411.035.8 + 117.656.5\ (0) = 411.035.8$

$y_1 = 411.035.8 + 117.656.5\ (1) = 528.692.3$

$y_2 = 411.035.8 + 117.656.5\ (2) = 646.348.8$

$= 2.055.179$

2. Ecuación Parabólica

$yc = a + bx + cx^2$

Año	X	y	x.y	x^2	$x^2.y$	x^4	yt	$(y-yt)^2$	S
1977	-2	211.242	-422.484	4	844.968	16	192.280.4	359.542.275	
1978	-1	236.745	-236.745	1	236.745	1	285.100.5	2.338.254.380	
1979	0	425.775	0	0	0	0	394.478.2	979.489.690	
1980	1	527.040	527.040	1	527.040	1	520.413.5	43.910.502	
1981	2	654.377	1.308.754	4	2.617.508	16	662.906.4	72.750.664	
	0	2.055.179	1.176.565	10	4.226.261	34	2.055.179	2.814.457.820	43.554

$yc = a + bx + cx^2$

Anexo 1: CONTINUACION

$$c = n\,x^2y - x^2y\,/\,n\,x^4 - (x^2)^2$$

$$c = 5(4.226.261) - 10(2.055.179)/5\,(34) - (10)^2 = 8.278.8$$

$$a = (y - c\,x^2)/n = 2.055.179 - 8.278.8(10)/5 = 394.478.2$$

$$b = xy/x^2 = 1.176.565/10 = 117.656.5$$

$$yc = a + bx + cx^2$$

$$yt = 394.478.2 + 117.656.5\,x + 8.278.8\,x^2$$

$$y_{-2} = 394.478.2 + 117.656.5\,(-2) + 8.278.8\,(-2)^2 = 192.280.4$$

$$y_{-1} = 394.478.2 + 117.656.5\,(-1) + 8.278.8\,(-1)^2 = 285.100.5$$

$$y_o = 394.478.2 + 117.656.5\,(0) + 8.278.8\,(0) = 394.478.2$$

$$y_1 = 394.478.2 + 117.656.5\,(1) + 8.278.8\,(1) = 520.413.5$$

$$y_2 = 394.478.2 + 117.656.5\,(2) + 8.278.8\,(2) = 662.906.4$$

$$= 2.065.179$$

3. Ecuación Exponencial

$$yc = a.b^x$$

AÑO	x	y	Log.y	x.log.y	x^2	Log.yc	yc	$(y - yt)^2$	S
1977	-2	211.242	5.32478	-10.64956	4	5.307252	202.886	70.660.836	
1978	-1	236.745	5.37428	- 5.37428	1	5.440216	275.560	1.506.604.225	
1979	0	425.775	5.62918	0	0	5.573180	374.266	2.653.177.081	
1980	1	527.040	5.72184	5.72184	1	5.706144	508.328	350.138.944	
1981	2	654.377	5.81582	11.63164	4	5.839108	690.411	1.298.449.156	
	0	2.055.179	27.86591	1.32964	10	27.86590	2.051.450	4.879.030.242	44.268

Anexo 1: CONTINUACION

Log. y_c = log. a + (log.b) x

Log. a = log.y /n = 27.86591/5 = 5.57318

Log. b = (x.log.y)/x^2 = 1.32964/10 = 0.132964

Log. y_c = 5.57318 + 0.132964 x

Log. y_{-2} = 5.57318 + 0.132964 (-2) = 5.307252

Log. y_{-1} = 5.57318 + 0.132964 (-1) = 5.440216

Log. y_o = 5.57318 + 0.132964 (0) = 5.57318

Log. y_1 = 5.57318 + 0.132964 (1) = 5.706144

Log. y_2 = 5.57318 + 0.132964 (2) = 5.839108

= 27.8659

AGUA ESTERIL AMPOLLA x 1cc.

AÑO	CONSUMO OBSERVADO	ECUACION LINEA RECTA (y=a+bx)	ECUACION PARABOLICA ($y=a+bx+cx^2$)	ECUACION EXPONENCIAL ($y = a.b^x$)
1977	211.242	175.723	192.280	202.886
1978	236.745	293.379	285.100	275.560
1979	425.775	511.036	394.478	374.266
1980	527.040	528.692	520.414	508.328
1981	654.377	646.349	662.906	690.411
	2'055.079	2'055.179	2'055.179	2'051.450
	Error típico	39.806	45.554	44.268

Anexo 1: CONTINUACION

Proyección Ecuación de Línea Recta

$y = a + bx$

$y = 411.035.8 + 117.656.5\ x$

Años	x	y
1985	6	1'116.975
1986	7	1'234.631
1987	8	1'352.288
1988	9	1'469.945
1989	10	1'587.601
1990	11	1'705.257.5
1991	12	1'822.914
1992	13	1'940.571
1993	14	2'058.227
1994	15	2'175.883

Anexo 1: CONTINUACION

AÑO	x	y	x.y	x^2	yt	$(y-yt)^2$	S
1977	-2	20.809	-41.618	4	16.104	22.108.804	
1978	-1	29.296	-29.296	1	28.454	708.964	
1979	0	32.124	0	0	40.801	75.290.329	
1980	1	49.167	49.167	1	53.149	15.856.324	
1981	2	72.610	145.220	4	65.496	50.616.110	
	0	204.006	123.473	10	204.006	164.580.531	7.407

$y = a + bx$

$a = y/n = 204.006/5 = 40.801.2$

$b = (xy)\ x^2 = 123.473/10 = 12.347.3$

$yt = 40.801.2 + 12.347.3\ (x)$

$y_{-2} = 40.801.2 + 12.347.2\ (-2) = 16.106.6$

$y_{-1} = 40.801.2 + 12.347.3\ (-1) = 28.453.9$

$y_0 = 40.801.2 + 12.347.3\ (0) = 40.801.2$

$y_1 = 40.801.2 + 12.347.3\ (1) = 53.148.5$

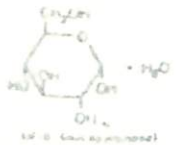
$y_2 = 40.801.2 + 12.347.3\ (2) = 65.495.8$

$= 204.006$

2. Ecuación Parabólica

$yt = a + bx + cx^2$

transfer 15.0 ml of this solution to a 25-ml
with 0.1 *N* hydrochloric acid to volume, and
determine the absorbances of this solution and
of USP Dextromethorphan Hydrobromide
having a known concentration of about 100
cells at the wavelength of maximum absorbance
with a suitable spectrophotometer, using 0.1 *N*
as the blank. Calculate the quantity, in mg, of
H_2O in each ml of the Syrup taken by the for-
(A_U/A_S), in which C is the concentration, in μg
Dextromethorphan Hydrobromide RS in the
V is the volume, in ml, of Syrup taken, and A_U
sorbances of the solution from the Syrup and the
respectively.



198.17
hydrate
hydrate [5996-*10-1*].
180.16 [50-99-7].

a sugar usually obtained by the hydrol-
ch. It contains one molecule of water of
is anhydrous.

rage—Preserve in well-closed containers.

it to indicate whether it is hydrous or anhy-

Add a few drops of a solution (1 in 20) to 5
tartrate TS: a copious red precipitate of cuprous

(781): between +52.5° and +53.0°, calculated
basis, determined in a solution containing 10 g
and 0.2 ml of 6 *N* ammonium hydroxide in each 100

— Dissolve 25 g in water to make 50.0 ml of solu-
tion has no more color than a solution prepared by
of cobaltous chloride CS, 3.0 ml of ferric chloride CS,
cupric sulfate CS with water to make 10 ml, and di-
this solution with water to 50 ml. Make the com-
ing the solutions downward in matched color-com-
against a white surface.

5.0 g in 50 ml of carbon dioxide-free water. Add
TS, and titrate with 0.020 *N* sodium hydroxide to
of a distinct pink color: not more than 0.30 ml is
neutralization.

III (921)—Dry it at 105° for 16 hours: the hy-
is between 7.5% and 9.5% of its weight, and the an-
not more than 0.5% of its weight.

(281): not more than 0.1%.

—A 2.0-g portion shows no more chloride than
0.50 ml of 0.020 *N* hydrochloric acid (0.018%).

A 2.0-g portion shows no more sulfate than corre-
50 ml of 0.020 *N* sulfuric acid (0.025%).

Dissolve 3.0 g in 35 ml of water and, in the *Pro-*
End of Standard Preparation instead of 10.0 ml. The

Dextrose Injection

» Dextrose Injection is a sterile solution of Dex
in Water for Injection. It contains not less than
percent and not more than 105.0 percent of the la
amount of $C_6H_{12}O_6 \cdot H_2O$. Dextrose Injection
tains no antimicrobial agents.

Packaging and storage—Preserve in single-dose containers,
erably of Type I or Type II glass.

Labeling—The label states the total osmolar concentration in
per liter. Where the contents are less than 100 ml, or whe
label states that the Injection is not for direct injection but is
diluted before use, the label alternatively may state the total os
concentration in mOsm per ml.

Identification—It responds to the *Identification test* under
trose.

Pyrogen—It meets the requirements of the *Pyrogen Test* (
[NOTE—Dilute, with water for injection, Injections conta
more than 10% of dextrose to give a concentration of 10% of
trose.]

pH (791): between 3.5 and 6.5, determined on a portion to w
0.30 ml of saturated potassium chloride solution has been adde
each 100 ml and which previously has been diluted with wate
necessary, to a concentration of not more than 5% of dextrose

Heavy metals (231)—Transfer a volume of Injection, equiva
to 4.0 g of dextrose, to a suitable vessel, and adjust the volum
25 ml by evaporation or addition of water, as necessary: the l
is 0.0005*C*%, in which *C* is the labeled amount, in g, of $C_6H_{12}O$
H_2O per ml of Injection.

5-Hydroxymethylfurfural and related substances—Dilute an
curately measured volume of Injection, equivalent to 1.0 g
$C_6H_{12}O_6 \cdot H_2O$, with water to 250.0 ml. Determine the absorba
of this solution in a 1-cm cell at 284 nm, with a suitable spect
photometer, using water as the blank: the absorbance is not m
than 0.25.

Other requirements—It meets the requirements under *Injecti*

Assay—Transfer an accurately measured volume of Dextrose
jection, containing 2 to 5 g of dextrose, to a 100-ml volumetric fla
Add 0.2 ml of 6 *N* ammonium hydroxide, dilute with water to v
ume, and mix. Determine the angular rotation in a suitable
larimeter tube at 25° (see (781)). The observed rotation, in d
grees, multiplied by 1.0425*A*, in which *A* is the ratio 200 divid
by the length, in mm, of the polarimeter tube employed, represe
the weight, in g, of $C_6H_{12}O_6 \cdot H_2O$ in the volume of Injecti
taken.

ANEXO 2

Dextrose Injection, Alcohol and—*see* Alcohol and Dextrose Injection

Dextrose and Sodium Chloride Injection

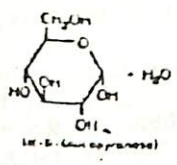
» Dextrose and Sodium Chloride Injection is a sterile
solution of Dextrose and Sodium Chloride in Water for
Injection. It contains not less than 95.0 percent and not
more than 105.0 percent of the labeled amount of
$C_6H_{12}O_6 \cdot H_2O$ and of NaCl. It contains no antimi-
crobial agents.

Packaging and storage—Preserve in single-dose containers, pref-
erably of Type I or Type II glass.

Labeling—The label states the total osmolar concentration in mOsm
[illegible] Where the contents are less than 100 ml, or where the
[illegible] is not for direct injection but is to be

in a 100-ml volumetric flask. Dilute with 0.1 *N* hydrochloric acid to volume, and mix. Transfer 15.0 ml of this solution to a 25-ml volumetric flask, dilute with 0.1 *N* hydrochloric acid to volume, and mix. Concomitantly determine the absorbances of this solution and of a Standard solution of USP Dextromethorphan Hydrobromide RS in the same medium having a known concentration of about 100 µg per ml in 1-cm cells at the wavelength of maximum absorbance at about 278 nm, with a suitable spectrophotometer, using 0.1 *N* hydrochloric acid as the blank. Calculate the quantity, in mg, of $C_{18}H_{25}NO \cdot HBr \cdot H_2O$ in each ml of the Syrup taken by the formula $(0.167C/V)(A_U/A_S)$, in which C is the concentration, in µg per ml, of USP Dextromethorphan Hydrobromide RS in the Standard solution, V is the volume, in ml, of Syrup taken, and A_U and A_S are the absorbances of the solution from the Syrup and the Standard solution, respectively.

Dextrose



$C_6H_{12}O_6 \cdot H_2O$ 198.17
D-Glucose, monohydrate.
D-Glucose monohydrate [*5996-10-1*].
Anhydrous 180.16 [*50-99-7*].

» Dextrose is a sugar usually obtained by the hydrolysis of Starch. It contains one molecule of water of hydration or is anhydrous.

Packaging and storage—Preserve in well-closed containers.

Labeling—Label it to indicate whether it is hydrous or anhydrous.

Identification—Add a few drops of a solution (1 in 20) to 5 ml of hot alkaline cupric tartrate TS: a copious red precipitate of cuprous oxide is formed.

Specific rotation ⟨781⟩: between +52.5° and +53.0°, calculated on the anhydrous basis, determined in a solution containing 10 g of Dextrose and 0.2 ml of 6 *N* ammonium hydroxide in each 100 ml.

Color of solution—Dissolve 25 g in water to make 50.0 ml of solution: the solution has no more color than a solution prepared by mixing 1.0 ml of cobaltous chloride CS, 3.0 ml of ferric chloride CS, and 2.0 ml of cupric sulfate CS with water to make 10 ml, and diluting 3 ml of this solution with water to 50 ml. Make the comparison by viewing the solutions downward in matched color-comparison tubes against a white surface.

Acidity—Dissolve 5.0 g in 50 ml of carbon dioxide–free water. Add phenolphthalein TS, and titrate with 0.020 *N* sodium hydroxide to the production of a distinct pink color: not more than 0.30 ml is required for neutralization.

Water, *Method III* ⟨921⟩—Dry it at 105° for 16 hours: the hydrous form loses between 7.5% and 9.5% of its weight, and the anhydrous form loses not more than 0.5% of its weight.

Residue on ignition ⟨281⟩: not more than 0.1%.

Chloride ⟨221⟩—A 2.0-g portion shows no more chloride than corresponds to 0.50 ml of 0.020 *N* hydrochloric acid (0.018%).

Sulfate ⟨221⟩—A 2.0-g portion shows no more sulfate than corresponds to 0.50 ml of 0.020 *N* sulfuric acid (0.025%).

Arsenic ⟨211⟩—Dissolve 3.0 g in 35 ml of water and, in the *Procedure*, use 3.0 ml of *Standard Preparation* instead of 10.0 ml. The limit is 1 ppm.

Heavy metals ⟨231⟩—Dissolve 4.0 g in water to make 25 ml of solution: the limit is 5 ppm.

Starch—Reflux 1 g of finely powdered Dextrose with 20 ml of alcohol: it dissolves completely.

Soluble starch, sulfites—To a solution of 1 g in 10 ml of water add a drop of Iodine TS: the liquid is colored yellow.

Dextrose Injection

» Dextrose Injection is a sterile solution of Dextrose in Water for Injection. It contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_6H_{12}O_6 \cdot H_2O$. Dextrose Injection contains no antimicrobial agents.

Packaging and storage—Preserve in single-dose containers, preferably of Type I or Type II glass.

Labeling—The label states the total osmolar concentration in mOsm per liter. Where the contents are less than 100 ml, or where the label states that the Injection is not for direct injection but is to be diluted before use, the label alternatively may state the total osmolar concentration in mOsm per ml.

Identification—It responds to the *Identification test* under *Dextrose*.

Pyrogen—It meets the requirements of the *Pyrogen Test* ⟨151⟩. [NOTE—Dilute, with water for injection, Injections containing more than 10% of dextrose to give a concentration of 10% of dextrose.]

pH ⟨791⟩: between 3.5 and 6.5, determined on a portion to which 0.30 ml of saturated potassium chloride solution has been added for each 100 ml and which previously has been diluted with water, if necessary, to a concentration of not more than 5% of dextrose.

Heavy metals ⟨231⟩—Transfer a volume of Injection, equivalent to 4.0 g of dextrose, to a suitable vessel, and adjust the volume to 25 ml by evaporation or addition of water, as necessary: the limit is 0.0005*C*%, in which *C* is the labeled amount, in g, of $C_6H_{12}O_6 \cdot H_2O$ per ml of Injection.

5-Hydroxymethylfurfural and related substances—Dilute an accurately measured volume of Injection, equivalent to 1.0 g of $C_6H_{12}O_6 \cdot H_2O$, with water to 250.0 ml. Determine the absorbance of this solution in a 1-cm cell at 284 nm, with a suitable spectrophotometer, using water as the blank: the absorbance is not more than 0.25.

Other requirements—It meets the requirements under *Injections* ⟨1⟩.

Assay—Transfer an accurately measured volume of Dextrose Injection, containing 2 to 5 g of dextrose, to a 100-ml volumetric flask. Add 0.2 ml of 6 *N* ammonium hydroxide, dilute with water to volume, and mix. Determine the angular rotation in a suitable polarimeter tube at 25° (see ⟨781⟩). The observed rotation, in degrees, multiplied by 1.0425*A*, in which *A* is the ratio 200 divided by the length, in mm, of the polarimeter tube employed, represents the weight, in g, of $C_6H_{12}O_6 \cdot H_2O$ in the volume of Injection taken.

Dextrose Injection, Alcohol and—*see* Alcohol and Dextrose Injection

Dextrose and Sodium Chloride Injection

» Dextrose and Sodium Chloride Injection is a sterile solution of Dextrose and Sodium Chloride in Water for Injection. It contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_6H_{12}O_6 \cdot H_2O$ and of NaCl. It contains no antimicrobial agents.

Packaging and storage—Preserve in single-dose containers, preferably of Type I or Type II glass.

Labeling—The label states the total osmolar concentration in mOsm per liter. Where the contents are less than 100 ml, or where the label states that the Injection is not for direct injection but is to be diluted before use, the label alternatively may state the total osmolar concentration in mOsm per ml.

Identification—It responds to the *Identification test* under *Dextrose*, and to the tests for *Sodium* ⟨191⟩ and for *Chloride* ⟨191⟩.

...It meets the requirements of the test for *Pyrogen* under ... *Injection*.

...ity: between 3.5 and 6.5, determined on a portion diluted ...ater, if necessary, to a concentration of not more than 5% of ...ose.

...ous amide—Arrange a train of 2 test tubes, the first being 200 ... mm and the second 150 × 25 mm in size, so that a current of ... can be passed through solutions contained in both tubes while ...first tube is immersed in a boiling water bath. Place 5 ml of ...ium hydroxide solution (1 in 50) in the second (smaller) tube, ...ce 45 ml of Injection in the first tube. With the first tube ...ed in the water bath, add to it 5 ml of dilute sulfuric acid (1 ... and close the system. Pass air through the solutions at the ... of 3 to 5 bubbles per second for 15 minutes. Remove the air ...tube from the second tube, rinse it with a small volume of water, ...1 drop of phenolphthalein TS, then add dilute hydrochloric acid ...5) until the pink color is discharged. Cool the neutralized ...ution to room temperature, add 0.2 ml of chloramine T solution ...ml), close the tube, and allow to stand for 1 minute. Add 6 ... pyridine-pyrazolone TS, mix, and allow the solution to stand ...30 minutes: the solution exhibits no blue color in comparison ...a reagent blank.

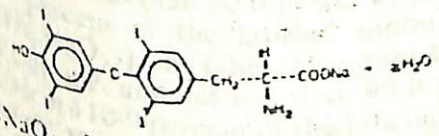
...ther requirements—It meets the requirements of the test for *Heavy ...als* under *Dextrose Injection*, and meets the requirements under ...ctions (1).

...ssay for dextrose—Transfer an accurately measured volume of ...ctrose and Sodium Chloride Injection, containing from 2 to 5 g ...dextrose, to a 100-ml volumetric flask. Add 0.2 ml of 6 *N* am-...nium hydroxide, dilute with water to volume, and mix. Deter-...ine the angular rotation in a suitable polarimeter tube at 25° (see ...ctrophotometry ⟨851⟩). The observed rotation, in degrees, multiplied by 1.0425*A*, ...in which *A* is the ratio 200 divided by the length, in mm, of the po-...rimeter tube employed, represents the weight, in g, of ...H_2O in the volume of Injection taken:

...ssay for sodium chloride—Transfer an accurately measured vol-...e of Dextrose and Sodium Chloride Injection, equivalent to about ...0 mg of sodium chloride, to a glass-stoppered flask, and add ...ter, if necessary, to make about 50 ml. Add, while agitating, 50.0 ...l of 0.1 *N* silver nitrate VS, then add 3 ml of nitric acid and 5 ml ...of nitrobenzene, and shake well. Add 2 ml of ferric ammonium ...ulfate TS, and titrate the excess silver nitrate with 0.1 *N* ammo-...nium thiocyanate VS. Each ml of 0.1 *N* silver nitrate is equivalent ...to 5.844 mg of NaCl.

...xtrose Tablets, Sodium Chloride and—*see* Sodium Chloride and Dextrose Tablets

Dextrothyroxine Sodium



...$C_{15}H_{10}I_4NNaO_4 \cdot xH_2O$

...L-Tyrosine, O-(4-hydroxy-3,5-diiodophenyl)-3,5-diiodo-, mono-...sodium salt hydrate.

...3,3′,5,5′-tetraiodothyronine sodium salt hydrate [*7054-08-2*].

...Anhydrous 798.86 [*137-53-1*].

...Dextrothyroxine Sodium contains not less than 97.0 ...percent and not more than 103.0 percent of $C_{15}H_{10}I_4NNaO_4$, calculated on the dried basis.

...Packaging and storage—Preserve in tight containers.

...Identification—

...A: Ignite about 50 mg in a platinum dish over a free flame: it ...decrepitates and liberates iodine vapors.

...B: Dissolve about 5 mg in a mixture of 1 drop of hydrochloric ...acid and 5 ml of dilute alcohol (1 in 2), add 1 drop of sodium nitrite ...TS, dilute with water (1 in 10), and boil: a yellow color is produced. Cool, and ...render the solution alkaline by the addition of 6 *N* ammonium hy-...droxide: the color changes from yellow to red.

Specific rotation ⟨781⟩: between +5° and +6°, determined in a mixture of 1 volume of sodium hydroxide solution (1 in 25) and 2 volumes of alcohol, containing the equivalent of 0.30 g of anhydrous dextrothyroxine sodium in each 10 ml, calculated on the dried basis.

Loss on drying ⟨731⟩—Dry it at a pressure not exceeding 10 mm of mercury over phosphorus pentoxide at 60° for 4 hours: it loses not more than 11.0% of its weight.

Soluble halides—Shake 10 mg with 10 ml of water containing 1 drop of 2 *N* nitric acid for 5 minutes, filter, dilute the filtrate with water to 10 ml, and add 3 drops of silver nitrate TS: any turbidity produced is not greater than that of a control containing 0.10 ml of 0.020 *N* hydrochloric acid (0.7% as chloride).

Assay—Weigh accurately about 25 mg of Dextrothyroxine Sodium, and proceed as directed under *Oxygen Flask Combustion* ⟨471⟩, using 10 ml of sodium hydroxide solution (1 in 1250) as the absorbing liquid. After combustion is complete, allow the flask to cool, shake vigorously to complete the absorption, and allow the vapors to settle. Place a few ml of water in the cup top, carefully withdraw the stopper, and rinse the stopper, platinum wire, platinum gauze, and sides of the flask with about 20 ml of water, added in small portions. Add 5 to 10 ml of a solution prepared by adding 10 g of potassium acetate and 0.40 ml of bromine to sufficient glacial acetic acid to make 100 ml. Allow to stand for 2 minutes, then add 1 ml of 90% formic acid, and rinse the sides of the flask with small portions of water. Add 1 g of potassium iodide, and titrate with 0.1 *N* sodium thiosulfate VS, adding 3 ml of starch TS as the end-point is approached. Each ml of 0.1 *N* sodium thiosulfate is equivalent to 3.329 mg of $C_{15}H_{10}I_4NNaO_4$.

Dextrothyroxine Sodium Tablets

» Dextrothyroxine Sodium Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{15}H_{10}I_4NNaO_4$.

Packaging and storage—Preserve in well-closed containers.

Identification—To an amount of finely powdered Tablets, equivalent to about 0.5 mg of dextrothyroxine sodium, add a mixture of 3 ml of dilute alcohol (1 in 2) and 0.2 ml of hydrochloric acid, and boil gently for 30 seconds. Cool, add 0.1 ml of sodium nitrite solution (1 in 10), and boil: a yellow color is produced. Cool, and render the solution alkaline by the addition of 6 *N* ammonium hydroxide: the color changes from yellow to orange.

Disintegration ⟨701⟩: 30 minutes.

Content uniformity ⟨681⟩: meet the requirements for *Tablets*.

Assay—Weigh and finely powder not less than 20 Dextrothyroxine Sodium Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 3 mg of dextrothyroxine sodium, to a large nickel crucible, add an amount of anhydrous potassium carbonate equivalent to twice the weight of the powder taken (but in no case less than 8 g), mix, and compact the mixture by gently tapping the crucible. Overlay the mixture with 10 g of anhydrous potassium carbonate, compact the charge by tapping the crucible, and ignite in a muffle furnace at 675° to 700° for 25 minutes. Cool the crucible, add 20 ml of water, heat gently to boiling, and decant the hot solution through a filter into a 500-ml conical flask. Repeat the extraction with an additional 20 ml of water, passing the hot solution through the same filter, and wash the crucible and filter with hot water until the filtrate in the flask measures about 200 ml. Cautiously add 40 ml of dilute phosphoric acid (1 in 2), followed by 7 ml of freshly prepared bromine TS, and then boil until starch iodide paper no longer is colored blue by the vapors. During the boiling, add water as necessary to maintain a volume of at least 200 ml. Rinse the walls of the flask with water, continue boiling for 5 minutes, cool, add 5 ml of phenol solution (1 in 20), again rinse the walls of the flask with water, and allow to stand for 5 minutes. Add 2 ml of dilute phosphoric acid (1 in 2) and 5 ml of potassium iodide TS, and titrate immediately with 0.01 *N* sodium thiosulfate VS from a 10-ml buret, adding 3 ml of starch TS as the end-point is approached. Perform a blank determination, and make any necessary correction. Each ml of 0.01 *N* sodium thiosulfate is equivalent to 0.3329 mg of $C_{15}H_{10}I_4NNaO_4$.

...oxo-3-[[(4-methyl-1-piperazinyl)amino]methyl]-...-15,19,21-Hexahydroxy-23-methoxy-2,4,12,16,18,20,22-...-pentamethyl-8-[*N*-(4-methyl-1-piperazinyl)formimidoyl]-...-epoxypentadeca[1,11,13]trieniimino)naphtho[2,1-*b*]-...furan-1,11-(2*H*)-dione 21-acetate [*13292-46-1*].

» Rifampin conforms to the regulations of the federal ...d and Drug Administration concerning antibiotic ...gs (455.70) (see *Antibiotics* (1011)). It has a po...cy of not less than 900 µg of $C_{43}H_{58}N_4O_{12}$ per ...g.

Packaging and storage—Preserve in tight, light-resistant containers, ...otected from excessive heat.

Reference standard—*U.S. Rifampin Reference Standard.*

pH: between 4.0 and 6.0, in a 1% aqueous suspension.

Loss on drying: not more than 2%.

Absorptivity: at 475 nm, between 96% and 104%, calculated on the ...ydrous basis, of that of the U.S. Rifampin Reference Standard, ...ilarly treated.

Other requirements—It complies with the tests for identification, ...olarity, and crystallinity.

Rifampin Capsules

» Rifampin Capsules conform to the regulations of the federal Food and Drug Administration concerning antibiotic drugs (455.170a) (see *Antibiotics* (1011)). Capsules contain not less than 90.0 percent and not more than 130.0 percent of the labeled amount of $C_{43}H_{58}N_4O_{12}$, the labeled amount being 300 mg in each Capsule.

Packaging and storage—Preserve in tight, light-resistant containers, ...otected from excessive heat.

Loss on drying: not more than 3.0%.

Rifampin and Isoniazid Capsules

» Rifampin and Isoniazid Capsules conform to the ...egulations of the federal Food and Drug Administration concerning antibiotic drugs (455.170b) (see *Antibiotics* (1011)). Rifampin and Isoniazid Capsules ...contain not less than 90.0 percent and not more than 130.0 percent of the labeled amount of rifampin ($C_{43}H_{58}N_4O_{12}$), the labeled amount being 300 mg in each Capsule, and not less than 90.0 percent and not more than 110.0 percent of the labeled amount of isoniazid ($C_6H_7N_3O$), the labeled amount being 150 mg in each Capsule.

Packaging and storage—Preserve in tight, light-resistant containers, ...avoid exposure to excessive heat.

Loss on drying: not more than 3.0%.

Ringer's Injection

» Ringer's Injection is a sterile solution of Sodium ...loride, Potassium Chloride, and Calcium Chloride ...Water for Injection. It contains, in each 100 ml, not ...ss than 323.0 mg and not more than 354.0 mg of so...um (Na, equivalent to not less than 820.0 mg and not ...re than 900.0 mg of NaCl); not less than 14.9 mg ...d not more than 16.5 mg of potassium (K, equivalent to not less than 28.5 mg and not more than 31.5 mg of KCl); not less than 8.20 mg and not more than 9.80 mg of calcium (Ca, equivalent to not less than 30.0 mg and not more than 36.0 mg of $CaCl_2 \cdot 2H_2O$); and not less than 523.0 mg and not more than 580.0 mg of chloride (Cl, as NaCl, KCl, and $CaCl_2 \cdot 2H_2O$). Ringer's Injection contains no antimicrobial agents.

NOTE—The calcium, chloride, potassium, and sodium ion contents of Ringer's Injection are approximately 4.5, 156, 4, and 147.5 milliequivalents per liter, respectively.

Sodium Chloride	8.6 g
Potassium Chloride	0.3 g
Calcium Chloride	0.33 g
Water for Injection, a sufficient quantity, to make	1000 ml

Dissolve the three salts in the Water for Injection, filter until clear, place in suitable containers, and sterilize.

Packaging and storage—Preserve in single-dose containers, preferably of Type I or Type II glass.

Labeling—The label states the total osmolar concentration in mOsm per liter. Where the contents are less than 100 ml, or where the label states that the Injection is not for direct injection but is to be diluted before use, the label alternatively may state the total osmolar concentration in mOsm per ml.

Identification—It responds to the tests for *Sodium* (191) and for *Chloride* (191), and when concentrated to one-half its original volume, to the test for *Calcium* (191) and to the flame test for *Potassium* (191).

Pyrogen—It meets the requirements of the *Pyrogen Test* (151).

pH (791): between 5.0 and 7.5.

Arsenic (211)— Use 37.5 ml of Injection: the limit is 0.08 ppm.

Ferrocyanide—Proceed with Ringer's Injection as directed in the test for *Ferrocyanide* under *Dextrose and Sodium Chloride Injection*, except to use 42 ml of Injection.

Heavy metals (231)—Evaporate 67 ml to a volume of about 20 ml, add 2 ml of 1 *N* acetic acid, and dilute with water to 25 ml: the limit is 0.3 ppm.

Other requirements—It meets the requirements under *Injections* (1).

Assay for calcium—Pipet 50 ml of Ringer's Injection into a 250-ml beaker, add 15 ml of 1 *N* sodium hydroxide and 300 mg of hydroxy naphthol blue indicator, and titrate immediately with 0.005 *M* disodium ethylenediaminetetraacetate VS to a deep blue end-point. Each ml of 0.005 *M* disodium ethylenediaminetetraacetate is equivalent to 200.4 µg of Ca^{++}.

Assay for potassium—

Standard stock solution—Dissolve 190.7 mg of potassium chloride, previously dried at 105° for 2 hours, in 50 ml of water, transfer to a 1000-ml volumetric flask, dilute with water to volume, and mix. Each ml of this solution contains 100 µg of potassium.

Standard preparations—Dissolve 1.093 g of sodium chloride in 100.0 ml of water, and transfer 10 ml of this solution to each of five 100-ml volumetric flasks containing 10.0 ml of a solution of a suitable nonionic wetting agent (1 in 500). Dilute the contents of one of the flasks with water to volume to provide a blank. To the remaining flasks add, respectively, 5.0, 10.0, 15.0, and 20.0 ml of *Standard stock solution*, dilute with water to volume, and mix.

Assay preparation—Pipet 10 ml of Ringer's Injection into a 100-ml volumetric flask, add 10.0 ml of a solution of a suitable wetting agent (1 in 500), dilute with water to volume, and mix.

Standard graph—Set a suitable flame photometer for maximum transmittance at a wavelength of about 766 nm. Adjust the instrument to zero transmittance with the blank. Adjust the instrument to 100% transmittance with the most concentrated of the *Standard preparations*. Read the percentage transmittance of the other *Standard preparations*, and plot transmittances versus concentration of potassium.

Procedure—Adjust the instrument as directed under *Standard graph*, read the percentage transmittance of the *Assay preparation*,

and calculate the potassium content, in mg per 100 ml, of Ringer's Injection.

Assay for sodium—

Standard stock solution—Dissolve 254.2 mg of sodium chloride, previously dried at 105° for 2 hours, in 50 ml of water, transfer to a 1000-ml volumetric flask, dilute with water to volume, and mix. Each ml of this solution contains 100 μg of sodium.

Standard preparations—Transfer to each of five 100-ml volumetric flasks 10 ml of a solution of a suitable nonionic wetting agent (1 in 500). Dilute the contents of one of the flasks with water to volume to provide a blank. To the remaining flasks add, respectively, 5.0, 10.0, 15.0, and 20.0 ml of *Standard stock solution*, dilute with water to volume, and mix.

Assay preparation—Pipet 5 ml of Ringer's Injection into a 1000-ml volumetric flask containing 100 ml of a solution of a suitable wetting agent (1 in 500), dilute with water to volume, and mix.

Procedure—Proceed as directed for *Standard graph* and for *Procedure* in the *Assay for potassium*, setting the flame photometer for maximum transmittance at a wavelength of about 589 nm, instead of about 766 nm. Calculate the sodium content, in mg per 100 ml, of Ringer's Injection.

Assay for chloride—Pipet 20 ml of Ringer's Injection into a glass-stoppered flask, and add 25 ml of water and 3 ml of nitric acid. While agitating the mixture, slowly add 50.0 ml of 0.1 *N* silver nitrate VS. Add 5 ml of nitrobenzene, shake vigorously for 1 minute, add 2 ml of ferric ammonium sulfate TS, and titrate the excess silver nitrate with 0.1 *N* ammonium thiocyanate VS. Each ml of 0.1 *N* silver nitrate is equivalent to 3.545 mg of Cl.

Lactated Ringer's Injection

» Lactated Ringer's Injection is a sterile solution of Calcium Chloride, Potassium Chloride, Sodium Chloride, and Sodium Lactate in Water for Injection. It contains, in each 100 ml, not less than 285.0 mg and not more than 315.0 mg of sodium (as NaCl and $C_3H_5NaO_3$), not less than 14.1 mg and not more than 17.3 mg of potassium (K, equivalent to not less than 27.0 mg and not more than 33.0 mg of KCl), not less than 4.90 mg and not more than 6.00 mg of calcium (Ca, equivalent to not less than 18.0 mg and not more than 22.0 mg of $CaCl_2 \cdot 2H_2O$), not less than 368.0 mg and not more than 408.0 mg of chloride (Cl, as NaCl, KCl, and $CaCl_2 \cdot 2H_2O$), and not less than 231.0 mg and not more than 261.0 mg of lactate ($C_3H_5O_3$, equivalent to not less than 290.0 mg and not more than 330.0 mg of $C_3H_5NaO_3$). Lactated Ringer's Injection contains no antimicrobial agents.

NOTE—The calcium, potassium, and sodium contents of Lactated Ringer's Injection are approximately 2.7, 4, and 130 milliequivalents per liter, respectively.

Packaging and storage—Preserve in single-dose containers, preferably of Type I or Type II glass.

Labeling—Solutions of higher concentrations of the specified constituents of Lactated Ringer's Injection, in which the ratios of the components are consistent with the official limits, may be labeled "For the preparation of Lactated Ringer's Injection USP," provided that the label indicates also that the solution is a concentrate, and that directions are given for dilution to the official strength.

The label states the total osmolar concentration in mOsm per liter. Where the contents are less than 100 ml, or where the label states that the Injection is not for direct injection but is to be diluted before use, the label alternatively may state the total osmolar concentration in mOsm per ml. The label includes also the warning: "Not for use in the treatment of lactic acidosis."

Identification—It responds to the tests for *Sodium* (191), for *Chloride* (191), and for *Lactate* (191), and when concentrated to one-half its original volume, to the test for *Calcium* (191) and to the flame test for *Potassium* (191).

Pyrogen—It meets the requirements of the *Pyrogen Test* (151).

pH (791): between 6.0 and 7.5.

Arsenic (211)—Use 37.5 ml of Injection: the limit is 0.08 ppm.

Ferrocyanide—Proceed as directed in the test for *Ferrocyanide* under *Dextrose and Sodium Chloride Injection*, except to use only 40 ml of the Injection.

Heavy metals (231)—Evaporate 67 ml to a volume of 20 ml, add 2 ml of 1 *N* acetic acid, then dilute with water to 25 ml: the limit is 0.3 ppm.

Other requirements—It meets the requirements under *Injections* (1).

Assay for calcium—Proceed with Lactated Ringer's Injection as directed in the *Assay for calcium* under *Ringer's Injection*.

Assay for potassium—Proceed with Lactated Ringer's Injection as directed in the *Assay for potassium* under *Ringer's Injection*.

Assay for sodium—Proceed with Lactated Ringer's Injection as directed in the *Assay for sodium* under *Ringer's Injection*.

Assay for chloride—Proceed with Lactated Ringer's Injection as directed in the *Assay for chloride* under *Ringer's Injection*.

Assay for lactate—Evaporate 50.0 ml of Lactated Ringer's Injection in a suitable crucible or dish, and ignite gently until thoroughly charred. Break up the charred mass well with a glass rod, add 25 ml of water and 25.0 ml of 0.1 *N* sulfuric acid VS, and heat on a steam bath for 30 minutes, breaking up any lumps with a glass rod during the heating. Filter, wash well with hot water until the last washing is neutral to litmus paper, then cool the combined filtrate and washings, add methyl orange TS, and titrate the excess acid with 0.1 *N* sodium hydroxide VS. Each ml of 0.1 *N* sulfuric acid is equivalent to 8.907 mg of $C_3H_5O_3$.

Ringer's Irrigation

» Ringer's Irrigation is a sterile solution of Sodium Chloride, Potassium Chloride, and Calcium Chloride in Water for Injection. It contains, in each 100 ml, not less than 323.0 mg and not more than 354.0 mg of sodium (Na, equivalent to not less than 820.0 mg and not more than 900.0 mg of NaCl); not less than 13.0 mg and not more than 18.0 mg of potassium (K, equivalent to not less than 25.0 mg and not more than 35.0 mg of KCl); not less than 8.20 mg and not more than 9.80 mg of calcium (Ca, equivalent to not less than 30.0 mg and not more than 36.0 mg of $CaCl_2 \cdot 2H_2O$); and not less than 523.0 mg and not more than 580.0 mg of chloride (Cl, as NaCl, KCl, and $CaCl_2 \cdot 2H_2O$).

Caution—Do not use Ringer's Irrigation for parenteral administration or for irrigations that may result in absorption of the Irrigation into the blood. For such purposes use Ringer's Injection.

Sodium Chloride	8.6 g
Potassium Chloride	0.3 g
Calcium Chloride	0.33 g
Water for Injection, a sufficient quantity, to make	1000 ml

Dissolve the three salts in Water for Injection to make 1000 ml, and filter until clear.

Packaging and storage—Preserve in single-dose containers, preferably of Type I or Type II glass. The container may be designed to empty rapidly and may contain a volume of more than 1 liter.

Labeling—The designation "not for injection" appears prominently on the label.

Pyrogen—It meets the requirements of the *Pyrogen Test* (151).

Sterility—It meets the requirements under *Sterility Tests* (71).

pH (791): between 5.0 and 7.5.

Identification—

A: The solution employed for measurement of absorbance in the *Assay* exhibits absorbance maxima and minima in the ultraviolet region at the same wavelengths as those of the Standard solution prepared as directed in the *Assay*.

B: Triturate a quantity of finely powdered Tablets, equivalent to about 200 mg of warfarin sodium, with 50 ml of water, centrifuge, and filter the supernatant liquid. Extract with 50 ml of ether, transfer the aqueous layer to a second separator, and discard the ether. Adjust with hydrochloric acid to a pH of less than 3, using short-range pH indicator paper, and extract with 50 ml of chloroform. Transfer the chloroform layer to another separator, extract with 50 ml of sodium hydroxide solution (1 in 250), and discard the chloroform. Transfer the aqueous layer to a beaker, and adjust with hydrochloric acid to a pH of less than 3 (using the pH indicator paper) to precipitate the warfarin. Filter, and wash the precipitate with four 5-ml portions of water. If the precipitate is not white or practically white, dissolve it in a minimum volume of sodium hydroxide solution (1 in 250), dilute with water to 50 ml, and repeat the foregoing procedure, beginning with "Extract with 50 ml of ether." Dry the precipitate in vacuum over phosphorus pentoxide for 4 hours: the infrared absorption spectrum of the warfarin so obtained exhibits maxima only at the same wavelengths as that of a similar preparation of USP Warfarin RS.

C: Dissolve a quantity of finely powdered Tablets, equivalent to about 100 mg of warfarin sodium, in 25 ml of water, and filter, if necessary: a 5-ml portion of the filtrate responds to the tests for *Sodium* ⟨191⟩.

Disintegration ⟨701⟩: 30 minutes.

Content uniformity ⟨681⟩: meet the requirements for *Tablets*.

Assay—Weigh and finely powder not less than 20 Warfarin Sodium Tablets. Weigh accurately a portion of the powder, equivalent to about 40 mg of warfarin sodium, and transfer to a 250-ml volumetric flask. Add 50 ml of sodium hydroxide solution (1 in 2500), shake for about 15 minutes, then add sodium hydroxide solution (1 in 2500) to volume. Filter through paper, discarding the first 20 ml of the filtrate. Pipet 10 ml of the subsequent filtrate into a 125-ml separator, add 2 ml of water, adjust with hydrochloric acid to a pH of less than 3, using short-range pH indicator paper, and extract with one 25-ml and two 15-ml portions of chloroform, filtering each through a pledget of glass wool into a 100-ml volumetric flask. Rinse the pledget, and add chloroform to volume. Dissolve an accurately weighed quantity of USP Warfarin RS, in chloroform, and dilute quantitatively and stepwise with chloroform to obtain a Standard solution having a known concentration of about 15 μg per ml. Concomitantly determine the absorbances of both solutions in 1-cm cells at the wavelength of maximum absorbance at about 307 nm, with a suitable spectrophotometer, using chloroform as the blank. Calculate the quantity, in mg, of $C_{19}H_{15}NaO_4$ in the portion of Tablets taken by the formula $2.5C(1.071A_U/A_S)$, in which C is the concentration, in μg per ml, of USP Warfarin RS in the Standard solution, 1.071 is the ratio of the molecular weight of warfarin sodium to that of warfarin, and A_U and A_S are the absorbances of the solution from Warfarin Sodium Tablets and the Standard solution, respectively.

Water for Injection

» Water for Injection is Water purified by distillation or by reverse osmosis. It contains no added substance.

Caution—Water for Injection is intended for use as a solvent for the preparation of parenteral solutions. For parenteral solutions that are prepared under aseptic conditions and are not sterilized by appropriate filtration or in the final container, first render the Water for Injection sterile and thereafter protect it from microbial contamination.

Packaging and storage—Preserve in tight containers. It may be stored at a temperature below or above the range in which microbial growth occurs.

Endotoxin—When previously rendered isotonic by the addition of 900 mg of pyrogen-free sodium chloride for each 100 ml, it meets the requirements of the *Pyrogen Test* ⟨151⟩.

Other requirements—It meets the requirements of the other tests under *Purified Water*, with the exception of the test for *Bacteriological purity*.

Bacteriostatic Water for Injection

» Bacteriostatic Water for Injection is Sterile Water for Injection containing one or more suitable antimicrobial agents.

Note—Use Bacteriostatic Water for Injection with due regard for the compatibility of the antimicrobial agent or agents it contains with the particular medicinal substance that is to be dissolved or diluted.

Packaging and storage—Preserve in single-dose or in multiple-dose containers, preferably of Type I or Type II glass, of not larger than 30-ml size.

Labeling—Label it to indicate the name(s) and proportion(s) of the added antimicrobial agent(s).

Antimicrobial agent(s)—It meets the requirements under *Antimicrobial Preservatives—Effectiveness* ⟨51⟩, and meets the labeled claim for content of the antimicrobial agent(s), as determined by the method set forth under *Antimicrobial Agents—Content* ⟨341⟩.

Pyrogen—When previously rendered isotonic by the addition of 900 mg of pyrogen-free sodium chloride for each 100 ml, it meets the requirements of the *Pyrogen Test* ⟨151⟩, the test dose being 5 ml per kg, injected very slowly.

Sterility—It meets the requirements under *Sterility Tests* ⟨71⟩.

pH ⟨791⟩: between 4.5 and 7.0, determined potentiometrically in a solution prepared by the addition of 0.30 ml of saturated potassium chloride solution to 100 ml of Bacteriostatic Water for Injection.

Chloride—It meets the requirements of the test for *Chloride* under *Sterile Water for Injection*, allowance being made for chloride derived from any chloride-containing added substance declared on the label.

Other requirements—It meets the requirements of the other tests under *Purified Water*, with the exception of those for *Ammonia*, *Oxidizable substances*, and *Bacteriological purity*.

Sterile Water for Inhalation

» Sterile Water for Inhalation is water purified by distillation or by reverse osmosis and rendered sterile. It contains no antimicrobial agents or other added substances.

Caution—Do not use Sterile Water for Inhalation for parenteral administration.

Packaging and storage—Preserve in single-dose containers.

Labeling—Label it to indicate that it is for inhalation therapy only and that it is not for parenteral administration.

pH ⟨791⟩: between 4.5 and 7.5, in a solution containing 0.30 ml of saturated potassium chloride solution per 100 ml of test specimen.

Sterility—It meets the requirements under *Sterility Tests* ⟨71⟩.

Chloride—To 20 ml in a color-comparison tube add 5 drops of nitric acid and 1 ml of silver nitrate TS, and gently mix: any turbidity formed within 10 minutes is not greater than that produced in a control consisting of 20 ml of *High-purity Water* (see under *Chemical Resistance—Glass Containers* ⟨661⟩), similarly treated, viewed downward over a dark surface with light entering the tubes from the sides.

Sterile Water for Injection

» Sterile Water for Injection is Water for Injection sterilized and suitably packaged. It contains no antimicrobial agent or other added substance.

Packaging and storage—Preserve in single-dose containers, preferably of Type I or Type II glass, of not larger than 1-liter size.

Labeling—Label it to indicate that no antimicrobial or other substance has been added, and that it is not suitable for intravascular injection without its first having been made approximately isotonic by the addition of a suitable solute.

Pyrogen—When previously rendered isotonic by the addition of 900 mg of pyrogen-free sodium chloride for each 100 ml, it meets the requirements of the *Pyrogen Test* ⟨151⟩.

Sterility—It meets the requirements under *Sterility Tests* ⟨71⟩.

Ammonia—For Sterile Water for Injection in glass containers of up to 50-ml size, dilute 50 ml with 50 ml of *High-purity Water* (see under *Reagents* in ⟨661⟩), and use this dilution as the test solution; for larger sizes, use 100 ml of Sterile Water for Injection as the test solution. To 100 ml of the test solution add 2 ml of alkaline mercuric-potassium iodide TS: any yellow color produced immediately is not darker than that of a control containing 30 µg of added NH_3 in *High-purity Water* (see under *Reagents* in ⟨661⟩) (0.6 ppm for Sterile Water for Injection packaged in containers of up to 50-ml size; 0.3 ppm for larger sizes).

Chloride—To 20 ml in a color-comparison tube add 5 drops of nitric acid and 1 ml of silver nitrate TS, and gently mix: any turbidity formed within 10 minutes is not greater than that produced in a similarly treated control consisting of 20 ml of *High-purity Water* (see under *Reagents* in ⟨661⟩) containing 10 µg of Cl (0.5 ppm), viewed downward over a dark surface with light entering the tubes from the sides.

Oxidizable substances—To 100 ml add 10 ml of 2 *N* sulfuric acid, and heat to boiling. For Sterile Water for Injection in containers of up to 50-ml size, add 0.4 ml of 0.1 *N* potassium permanganate, and boil for 5 minutes; for larger sizes, add 0.2 ml of 0.1 *N* potassium permanganate, and boil for 5 minutes: the pink color does not completely disappear.

Total solids—Proceed as directed in the test for *Total solids* under *Purified Water*. The following limits apply for Sterile Water for Injection in glass containers: up to and including 30-ml size, 0.003%; from 30-ml up to and including 100-ml size, 0.002%; for larger sizes, 0.002%.

Other requirements—It meets the requirements of the other tests under *Purified Water*, with the exception of the test for *Bacteriological purity*.

Sterile Water for Irrigation

» Sterile Water for Irrigation is Water for Injection that has been sterilized and suitably packaged. It contains no antimicrobial agent or other added substance.

Packaging and storage—Preserve in single-dose containers, preferably of Type I or Type II glass. The container may contain a volume of more than 1 liter, and may be designed to empty rapidly.

Labeling—Label it to indicate that no antimicrobial or other substance has been added. The designations "For irrigation only" and "Not for injection" appear prominently on the label.

Other requirements—It meets the requirements under *Sterile Water for Injection*.

Purified Water

H₂O
18.02

» Purified Water is water obtained by distillation, ion-exchange treatment, reverse osmosis, or other suitable process. It is prepared from water complying with the regulations of the federal Environmental Protection Agency with respect to drinking water. Purified Water contains no added substance.

Caution—Do not use Purified Water in preparations intended for parenteral administration. For such purposes use Water for Injection, Bacteriostatic Water for Injection, or Sterile Water for Injection.

Packaging and storage—Preserve in tight containers.

Labeling—Label it to indicate the method of preparation.

pH ⟨791⟩: between 5.0 and 7.0, determined potentiometrically in a solution prepared by the addition of 0.30 ml of saturated potassium chloride solution to 100 ml of Purified Water.

Chloride—To 100 ml add 5 drops of nitric acid and 1 ml of silver nitrate TS: no opalescence is produced.

Sulfate—To 100 ml add 1 ml of barium chloride TS: no turbidity is produced.

Ammonia—To 100 ml add 2 ml of alkaline mercuric-potassium iodide TS: any yellow color produced immediately is not darker than that of a control containing 30 µg of added NH_3 in *High-purity Water* (see under *Reagents* in ⟨661⟩) [0.3 ppm].

Calcium—To 100 ml add 2 ml of ammonium oxalate TS: no turbidity is produced.

Carbon dioxide—To 25 ml add 25 ml of calcium hydroxide TS: the mixture remains clear.

Heavy metals—Adjust 40 ml of Purified Water with 1 *N* acetic acid to a pH of 3.0 to 4.0 (using short-range pH indicator paper), add 10 ml of freshly prepared hydrogen sulfide TS, and allow the liquid to stand for 10 minutes: the color of the liquid, when viewed downward over a white surface, is not darker than the color of a mixture of 50 ml of the same Purified Water with the same amount of 1 *N* acetic acid as was added to the test specimen, matched color-comparison tubes being used for the comparison.

Oxidizable substances—To 100 ml add 10 ml of 2 *N* sulfuric acid, and heat to boiling. Add 0.1 ml of 0.1 *N* potassium permanganate, and boil for 10 minutes: the pink color does not completely disappear.

Total solids—Evaporate 100 ml on a steam bath to dryness, and dry the residue at 105° for 1 hour: not more than 1 mg of residue remains (0.001%).

Bacteriological purity—It complies with the federal Environmental Protection Agency regulations for drinking water with respect to bacteriological purity (40 CFR 141.14; 141.21).

Wax, Carnauba—*see* Wax, Carnauba NF

Wax, Cetyl Esters—*see* Cetyl Esters Wax NF

Wax, Emulsifying—*see* Wax, Emulsifying NF

Wax, Microcrystalline—*see* Wax, Microcrystalline NF

Wax, White—*see* Wax, White NF

Wax, Yellow—*see* Wax, Yellow NF

White Lotion

» Prepare White Lotion as follows.

Zinc Sulfate	40 g
Sulfurated Potash	40 g
Purified Water, a sufficient quantity, to make	1000 ml

Dissolve the Zinc Sulfate and the Sulfurated Potash separately, each in 450 ml of Purified Water, and filter each solution. Add the sulfurated potash solution slowly to the zinc sulfate solution with constant stirring. Then add the required amount of purified water, and mix.

GENERAL CHAPTERS

General Tests *and* Assays

General Requirements for Tests and Assays

⟨1⟩ INJECTIONS

Every care should be exercised in the preparation of all products intended for injection, to prevent contamination with microorganisms and foreign material. Good pharmaceutical practice requires also that each final container of Injection be subjected individually to a physical inspection, whenever the nature of the container permits, and that every container whose contents show evidence of contamination with visible foreign material be rejected.

Definitions—In this Pharmacopeia, the sterile preparations for parenteral use are grouped into five distinct classes, defined as follows: (1) medicaments or solutions or emulsions thereof suitable for injection, bearing titles of the form, ____ *Injection;* (2) dry solids or liquid concentrates containing no buffers, diluents, or other added substances, and which, upon the addition of suitable solvents, yield solutions conforming in all respects to the requirements for ____; (3) preparations the same as those described under (2) except that they contain one or more buffers, diluents, or other added substances, and which are distinguished by titles of the form, ____ *for Injection;* (4) solids which are suspended in a suitable fluid medium and which are not to be injected intravenously or into the spinal canal, distinguished by titles of the form, *Sterile* ____ *Suspension;* and (5) dry solids which, upon the addition of suitable vehicles, yield preparations conforming in all respects to the requirements for Sterile Suspensions, and which are distinguished by titles of the form, *Sterile* ____ *for Suspension.*

Where used in this Pharmacopeia, the designation *Large-volume intravenous solution* applies to an Injection that is intended for intravenous use and is packaged in containers holding 100 ml or more.

The Pharmacopeial definitions for sterile preparations for parenteral use generally do not apply in the case of the biologics, because of their special nature and licensing requirements (see *Biologics* ⟨1041⟩).

Aqueous Vehicles—The vehicles for aqueous Injections meet the requirements of the *Pyrogen Test* ⟨151⟩. *Water for Injection* generally is used as the vehicle, unless otherwise specified in the individual monograph. Sodium chloride may be added in amounts sufficient to render the resulting solution isotonic; and *Sodium Chloride Injection*, or *Ringer's Injection*, may be used in whole or in part instead of *Water for Injection* unless otherwise specified in the individual monograph. For conditions applying to other additives, see *Added Substances*, in this chapter.

Other Vehicles—Fixed oils used as vehicles for nonaqueous injections are of vegetable origin, are odorless or nearly so, and have no odor or taste suggesting rancidity. They meet the requirements of the test for *Solid paraffin* under *Mineral Oil*, the cooling bath being maintained at 10°, have a *Saponification value* of between 185 and 200 (see ⟨401⟩), have an *Iodine value* of between 79 and 128 (see ⟨401⟩), and meet the requirements of the following tests:

Unsaponifiable Matter—Reflux on a steam bath 10 ml of the oil with 15 ml of sodium hydroxide solution (1 in 6) and 30 ml of alcohol, with occasional shaking until the mixture becomes clear. Transfer the solution to a shallow dish, evaporate the alcohol on a steam bath, and mix the residue with 100 ml of water: a clear solution results.

Free Fatty Acids—The free fatty acids in 10 g of oil require for neutralization not more than 2.0 ml of 0.020 *N* sodium hydroxide (see ⟨401⟩).

Synthetic mono- or diglycerides of fatty acids may be used as vehicles, provided they are liquid and remain clear when cooled to 10° and have an *Iodine value* of not more than 140 (see ⟨401⟩).

These and other nonaqueous vehicles may be used, provided they are safe in the volume of injection administered, and also provided they do not interfere with the therapeutic efficacy of the preparation or with its response to prescribed assays and tests.

Added Substances—Suitable substances may be added to preparations intended for injection to increase stability or usefulness, unless proscribed in the individual monograph, provided they are harmless in the amounts administered and do not interfere with the therapeutic efficacy or with the responses to the specified assays and tests. No coloring agent may be added, solely for the purpose of coloring the finished preparation, to a solution intended for parenteral administration (see also *Added Substances* under *General Notices*, and *Antimicrobial Preservatives—Effectiveness* ⟨51⟩).

Observe special care in the choice and use of added substances in preparations for injection that are administered in a volume exceeding 5 ml. The following maximum limits prevail unless otherwise directed: for agents containing mercury and the cationic, surface-active compounds, 0.01%; for those of the types of chlorobutanol, cresol, and phenol, 0.5%; and for sulfur dioxide, or an equivalent amount of the sulfite, bisulfite, or metabisulfite of potassium or sodium, 0.2%.

A suitable substance or mixture of substances to prevent the growth of microorganisms must be added to preparations intended for injection that are packaged in multiple-dose containers, regardless of the method of sterilization employed, unless otherwise directed in the individual monograph, or unless the active ingredients are themselves bacteriostatic. Such substances are used in concentrations that will prevent the growth of or kill microorganisms in the preparations for injection (see also *Antimicrobial Preservatives—Effectiveness* ⟨51⟩ and *Antimicrobial Agents—Content* ⟨341⟩). Sterilization processes are employed even though such substances are used (see also *Parenteral and Topical Preparations* in the section, *Added Substances*, under *General Notices*, and

Sterilization (1211)). The air in the container may be evacuated or be displaced by a chemically inert gas.

Containers for Injections—Containers, including the closures, for preparations for injection do not interact physically or chemically with the preparations in any manner to alter the strength, quality, or purity beyond the official requirements under the ordinary or customary conditions of handling, shipment, storage, sale, and use. The container is made of material that permits inspection of the contents. The type of glass preferable for each parenteral prepa ation is usually stated in the individual monograph.

For definitions of single-dose and multiple-dose containers, see Containers under *General Notices*. Containers meet the require ments under *Containers* (661).

Containers are closed by fusion, or by application of suitable closures, in such manner as to prevent contamination or loss of contents. Closures for multiple-dose containers permit the with drawal of the contents without removal or destruction of the closure. The closure permits penetration by a needle, and, upon withdrawal of the needle, at once recloses the container against contamination.

Containers for Sterile Solids—Containers, including the closures, for dry solids intended for parenteral use do not interact physically or chemically with the preparation in any manner to alter the strength, quality, or purity beyond the official requirements under ordinary or customary conditions of handling, shipment, storage, sale and use.

A container for a sterile solid permits the addition of a suitable solvent and withdrawal of portions of the resulting solution or suspension in such manner that the sterility of the product is maintained.

Volume in Container—Each container of an Injection is filled with a volume in slight excess of the labeled "size" or that volume which is to be withdrawn. The excess volumes recommended in the accompanying table are usually sufficient to permit withdrawal and administration of the labeled volumes.

DETERMINATION OF VOLUME OF INJECTION IN CONTAINERS—Select 1 or more containers if the volume is 10 ml or more, 3 or more if the volume is more than 3 ml and less than 10 ml, or 5 if the volume is 3 ml or less. Take up individually the contents of each container selected into a dry hypodermic syringe of a rated capacity not exceeding three times the volume to be measured, and fitted with a 21-gauge needle not less than 2.5 cm (1 inch) in length. Expel any air bubbles from the syringe and needle, and then discharge the contents of the syringe, without applying the needle, into a standardized, dry cylinder (graduated to contain rather than to deliver the designated volumes) of such diameter that the volume to be measured occupies at least 40% of its rated volume. Alternatively, the contents of the syringe may be discharged into a dry, tared beaker, the volume, in ml, being calculated from the weight, in g, of Injection taken divided by its density. The measurement, provided that a separate, dry syringe assembly is used for each container. The content of containers holding 10 ml or more may be determined by means of opening them and transferring the contents directly into the graduated cylinder or tared beaker.

The volume is not less than the labeled volume in the case of containers examined individually or, in the case of 1-ml and 2-ml containers, is not less than the sum of the labeled volumes of the containers taken collectively.

For Injections in multiple-dose containers labeled to yield a specified number of doses of a stated volume, proceed as directed in the foregoing, using the same number of separate syringes as the number of doses specified. The volume is such that each syringe delivers not less than the stated dose.

For Injections containing oil, warm the containers, if necessary, and thoroughly shake them immediately before removing the contents. Cool to 25° before measuring the volume.

Labeled Size	Recommended Excess Volume	
	For Mobile Liquids	For Viscous Liquids
0.5 ml	0.10 ml	0.12 ml
1.0 ml	0.10 ml	0.15 ml
2.0 ml	0.15 ml	0.25 ml
5.0 ml	0.30 ml	0.50 ml
10.0 ml	0.50 ml	0.70 ml
20.0 ml	0.60 ml	0.90 ml
30.0 ml	0.80 ml	1.20 ml
50 ml or more	2%	3%

Sterility Tests—Preparations for injection meet the requirements under *Sterility Tests* (71).

Labeling—The term "labeling" designates all labels and other written, printed, or graphic matter upon an immediate container of a preparation or upon, or in, any package or wrapper in which it is enclosed, except any outer shipping container. The term "label" designates that part of the labeling upon the immediate container.

The label states the name of the preparation; in the case of a liquid preparation, the percentage content of drug or amount of drug in a specified volume; in the case of a dry preparation, the amount of *active* ingredient; the route of administration; a statement of storage conditions and an expiration date; the name of the manufacturer or distributor; and an identifying lot number. The lot number is capable of yielding the complete manufacturing history of the specific package, including all manufacturing, filling, sterilizing and labeling operations.

Where the individual monograph permits varying concentrations of active ingredients in the large-volume parenteral, the concentration of each ingredient named in the official title is stated as a part of the official title, e.g., Dextrose Injection 5%, or Dextrose (5%) and Sodium Chloride (0.2%) Injection.

The labeling includes the following information, if the complete formula is not specified in the individual monograph: (1) In the case of a liquid preparation, the percentage content of each ingredient or the amount of each ingredient in a specified volume, except that ingredients added to adjust to a given pH or to make the solution isotonic may be declared by name and a statement of their effect; and (2) in the case of a dry preparation or other preparation to which a diluent is intended to be added before use, the amount of each ingredient, the composition of recommended diluent(s) [the name(s) alone, if the formula is specified in the individual monograph], the amount to be used to attain a specific concentration of active ingredient and the final volume of solution so obtained, a brief description of the physical appearance of the constituted solution, directions for proper storage of the constituted solution, and an expiration date limiting the period during which the constituted solution may be expected to have the required or labeled potency if it has been stored as directed.

Containers for Injections that are intended for use as dialysis, hemofiltration, or irrigation solutions and that contain a volume of more than 1 liter are labeled to indicate that the contents are not intended for use by intravenous infusion.

Injections intended for veterinary use are labeled to that effect.

The container is so labeled that a sufficient area of the container remains uncovered for its full length or circumference to permit inspection of the contents.

Packaging and storage—The volume of Injection in single-dose containers provides the amount specified for parenteral administration at one time and in no case is more than sufficient to permit the withdrawal and administration of 1 liter.

Preparations intended for intraspinal, intracisternal, or peridural administration are packaged only in single-dose containers.

Unless otherwise specified in the individual monograph, a multiple-dose container contains a volume of Injection more than sufficient to permit the withdrawal of 30 ml.

Injections packaged for use as irrigation solutions or for hemofiltration or dialysis are exempt from the foregoing requirements relating to packaging. Containers for Injections packaged for use as hemofiltration or irrigation solutions may be designed to empty rapidly and may contain a volume of more than 1 liter.

Injections labeled for veterinary use are exempt from packaging and storage requirements concerning the limitation to single-dose containers and the limitation on the volume of multiple-dose containers.

CONSTITUTED SOLUTIONS

Sterile dosage forms from which constituted solutions are prepared for injection bear titles of the form, *Sterile* ——— *for Injection*. Since these dosage forms are constituted at the time

of use by the health-care practitioner, tests and standards pertaining to the solution as constituted for administration are not included in the individual monographs on sterile dry solids or liquid concentrates. However, in the interest of assuring the quality of injection preparations as they are actually administered, the following nondestructive tests are provided for demonstrating the suitability of constituted solutions when they are prepared just prior to use.

Completeness and Clarity of Solution—Constitute the solution as directed in the labeling supplied by the manufacturer for the sterile dry dosage form

A: The solid dissolves completely, leaving no visible residue of undissolved matter

B: The constituted solution is not significantly less clear than an equal volume of the diluent or of Purified Water contained in a similar vessel and examined similarly.

Particulate Matter—Constitute the solution as directed in the labeling supplied by the manufacturer for the sterile dry dosage form: the solution is essentially free from particles of foreign matter that can be observed on visual inspection.

LARGE-VOLUME INJECTIONS FOR SINGLE-DOSE INFUSION

Particulate Matter—Particulate matter consists of extraneous, mobile, undissolved substances, other than gas bubbles, unintentionally present in parenteral solutions. Limits for particulate matter are prescribed herein for individual containers, each of which holds a single-dose large-volume injection intended for administration by intravenous infusion. The limits do not apply to multiple-dose injections, nor to single-dose, small-volume injections, nor to injectable solutions constituted from sterile solids. Results obtained in examining a discrete unit or group of units for particulate matter cannot be extrapolated with certainty to other units that remain untested. Statistically sound sampling plans based upon a known set of given operational factors must be elaborated if valid inferences are to be drawn from observed data to characterize the level of particulate matter in a large group of units.

This test for particulate matter is suitable for revealing the presence of particles whose longest axis, or effective linear dimension, is 10.0 μm or greater. Alternative procedures or procedural details may be employed to measure particulate matter, provided the results obtained are of equivalent reliability. However, where a difference appears, or in the event of a dispute, only the result obtained by the procedure given in this Pharmacopeia is conclusive.

PROCEDURE—[NOTE—Throughout this procedure, use suitable, nonpowdered gloves and scrupulously clean glassware and equipment that have been rinsed successively with a warm solution of detergent, hot water, water, and isopropyl alcohol. Apply the water as a strong jet back and forth across the surface of the vertically held object, working slowly from top to bottom. Perform the rinsing with isopropyl alcohol under a laminar flow hood equipped with ultra-HEPA (high-efficiency particulate absolute) filters. Permit the objects to dry under the hood upstream of all other operations. Preferably, locate the hood in a separate room that is supplied with filtered, air-conditioned air, and maintained under positive pressure with respect to the surrounding area. Prior to conducting the test, clean the laminar flow hood (except the surfaces of the filter media) with an appropriate solvent. Maintain air-flow velocity at 90 ± 20 feet per minute.]

Membrane filter and assembly—Using forceps, remove a color contrast grid membrane filter from its container. Wash both sides of the membrane with a stream of water that has been further purified by filtration through a suitable membrane to remove particulate matter having an effective linear dimension greater than 5 μm, by holding the filter in a vertical position, and, starting at the top of the nongridded side, sweeping the stream back and forth across the surface, working slowly from top to bottom so that particles will be rinsed downward off the filter, and repeating the process on the gridded side. Place the membrane (grid side up) on the filter holder base, and install the filtering funnel on the base without sliding the funnel over the membrane filter. Invert the assembled unit, and wash the inside of the funnel for about 10 seconds with a jet of filtered water. Allow the water to drain, and place the unit on the filter flask.

Test preparation—Mix the solution by inverting the container 20 times. Thoroughly clean the outer surface of the container with a jet of water, and remove the closure carefully, avoiding contamination of the contents. Transfer 25 ml of the well-mixed solution to the funnel, allow to stand for 1 minute, and apply the vacuum and filter. Release the vacuum gently, and wash the inner walls of the funnel with a jet of 25 ml of the filtered water. Direct the jet of filtered water in such manner as to wash the walls of the funnel free from any particles that may have become lodged on the walls, but avoid directing the stream onto the filter surface. After turbulence has dissipated, vacuum-filter the rinsing. Carefully remove the upper section of the filter assembly while maintaining vacuum. Release the vacuum, and remove the membrane filter with forceps. Place the filter in a plastic Petri slide, using a very thin film of stopcock grease as pre-coating, if necessary to hold the filter flat and in place. Allow the filter to dry with the cover of the Petri slide slightly ajar. Cover the slide carefully on the micrometer stage of the microscope, and count the particles on the filter as described below.

Determination—Examine the entire membrane filter in a suitable microscope under 100× magnification with the incident light at an angle of 10° to 20°. Count the number of particles having effective linear dimensions equal to or larger than 10.0 μm and equal to or larger than 25.0 μm. Perform a blank determination, using a *Membrane filter and assembly*, as directed under *Test preparation*, beginning with "wash the inner walls of the funnel with a jet." Subtract the total counts obtained in the blank determination from the uncorrected total counts for the *Test preparations* and blanks may be examined as directed. If the blank determination yields more than 5 particles having effective linear dimension of 25.0 μm or greater, the operational environment is unsatisfactory and the test is invalid.

Interpretation—Duplicate *Test preparations* and blanks may be examined as directed. If the blank determination yields more than 5 particles having effective linear dimension of 25.0 μm or greater, the operational environment is unsatisfactory and the test is invalid.

The large-volume injection for single-dose infusion meets the requirements of the test if it contains not more than 50 particles per ml that are equal to or larger than 10.0 μm and not more than 5 particles per ml that are equal to or larger than 25.0 μm in effective linear dimension.

⟨11⟩ USP REFERENCE STANDARDS

Reference Standards

USP Reference Standards are established and released under the authority of the USPC Board of Trustees upon recommendation of the USP Reference Standards Committee, which passes on the selection and suitability of each lot. The critical characteristics of each lot of specimen selected for the standard are usually determined independently in three or more laboratories. The USP Drug Research and Testing Laboratory (see *Preface*) and the Food and Drug Administration laboratories participate in testing almost all new Standards and replacements for existing Standards. In addition, laboratories throughout the nation, both academic and industrial, participate in the testing.

Reference Standards are specifically required in many Pharmacopeial assays and tests. Originally introduced for the biological assays of USP X, the use of reference standards has been extended to the point where they are now required for numerous other procedures as well. This reflects the extensive use of modern chromatography and spectrophotometry, which require measurements relative to a reference standard in order to attain accurate and reproducible results.

USP Reference Standards are substances selected for their high purity, critical characteristics, and suitability for the intended purpose. Heterogeneous substances, of natural origin, also are designated "Reference Standards" where needed. Usually these are the counterparts of international standards.

Antibiotic reference standards distributed by the USPC have been designated by the federal Food and Drug Administration as identical to FDA working standards under the FDA certification procedures. USPC distributes both U.S. Reference Standards and USP Reference Standards for antibiotic substances. This difference in labeling the Standards is in effect only temporarily, and eventually all vials will bear the same title. Where a USP Reference Standard is called for, the corresponding substance labeled as a "U.S. Reference Standard" may be used, and vice versa.

Reference Standards currently labeled as "NF Reference Standards" will eventually all be designated and labeled as "USP Reference Standards" pursuant to the consolidation of USP and

Volumetric Flasks						
...ted volume, ml	10	25	50	100	250	500	1000
...of error, ml	0.02	0.03	0.05	0.08	0.12	0.15	0.30
...of error, %	0.20	0.12	0.10	0.08	0.05	0.03	0.03

Transfer Pipets						
...ated volume, ml	1	2	5	10	25	50	100
...of error, ml	0.003	0.006	0.01	0.02	0.03	0.05	0.08
...of error, %	0.60	0.30	0.20	0.20	0.12	0.10	0.08

Burets			
...ated volume, ml	10 ("micro" type)	25	50
...ations, ml	0.02	0.10	0.10
...of error, ml	0.02	0.03	0.05

...ation of the reproducibility of the instrument, divided by the ...ount to be weighed, does not exceed 0.001.

...t weight classification should be chosen so as to limit the error ...tities. This generally means that Class P weights can be used for ...ities greater than 100 mg, Class S-1 for quantities greater than ...ities greater than 20 mg, and Class M for ...ities greater than 10 mg. Quantities of less than 10 mg may ...ighed on balances having appropriate reproducibilities and ...ding to afford electrical or optical methods for accurately ...ding a 10-mg, full-scale range, after calibration with a 10-...Class M weight.

...the tolerances shown in the accompanying table are for new or ...ly adjusted weights. For weights that have been in use, the ...ances are somewhat larger, as follows:

...Class M—100-, 200-, 300-, and 500-mg denominations—10.5 ...and 200 μg for the group.

...Class S—100-mg and heavier denominations—Twice the values ...shown in the accompanying table (for individual and group).

...Class S-1—Same as shown in the accompanying table.

...Class P—For all weights—Twice the values shown in the ac...panying table.

...weights should be calibrated periodically, preferably against an ...suitable standard weight.

Tolerances for New Weights in Sets

Class M		Class S		Class S-1	Class P
Individual μg	Group μg	Individual μg	Group μg	Individual μg	Individual μg
500					
250		250		1000	2000
150		120		600	1200
100		74	154	450	900
50		74	"	350	700
34		74	"	250	500
34	65				360
34	"	54	105	180	300
34	"	54	"	150	260	
	"	54	"	130	200
		54	"	100	
5.4					
5.4	10.5				160
5.4	"	25	55	80	140
5.4	"	25	"	70	120
5.4	"	25	"	60	100
5.4		25	"	50	
5.4	10.5				85
5.4	"	14	34	42	75
5.4	"	14	"	38	70
5.4	"	14	"	35	60
5.4		14	"	30	
5.4	10.5				55
5.4	"	14	34	28	52
5.4	"	14	"	26	50
	"	14	"	25	50
		14	"	25	

...Not more than one-third of Class S-1 weights are in ...more than one-half of the tabulated tolerances.

Microbiological Tests

⟨51⟩ ANTIMICROBIAL PRESERVATIVES—EFFECTIVENESS

Antimicrobial preservatives are substances added to dosage forms to protect them from microbial contamination. They are used primarily in multiple-dose containers to inhibit the growth of microorganisms that may be introduced inadvertently during or subsequent to the manufacturing process. Antimicrobial agents should not be used solely to reduce the viable microbial count as a substitute for good manufacturing practice. Situations may arise, however, where their use may be required to minimize proliferation of microorganisms. It should be recognized that the presence of dead microorganisms or the metabolic by-products of living microorganisms may cause adverse reactions in sensitized persons.

Any antimicrobial agent may exhibit the protective properties of a preservative. However, all useful antimicrobial agents are toxic substances. For maximum protection of the consumer, the concentration of the preservative shown to be effective in the final packaged product should be considerably below the concentrations of the preservative that may be toxic to human beings.

The following tests are provided to demonstrate, in multiple-dose parenteral, otic, nasal, and ophthalmic products, the effectiveness of any added antimicrobial preservative(s), the presence of which is declared on the label of the product concerned. The tests and standards apply only to the product in the original, unopened container in which it was distributed by the producer.

Test Organisms—Use cultures of the following microorganisms*: *Candida albicans* (ATCC No. 10231), *Aspergillus niger* (ATCC No. 16404), *Escherichia coli* (ATCC No. 8739), *Pseudomonas aeruginosa* (ATCC No. 9027), and *Staphylococcus aureus* (ATCC No. 6538). Other microorganisms, in addition to those listed, may be included in the test on an optional basis, especially if it appears likely that such microorganisms may represent contaminants likely to be introduced during use of the article.

Media—For the initial cultivation of the test organisms, select an agar medium that is favorable to vigorous growth of the respective stock culture, such as Soybean-Casein Digest Agar Medium (see under *Microbial Limit Tests* ⟨61⟩).

Preparation of Inoculum—Preparatory to the test, inoculate the surface of a suitable volume of solid agar medium from a recently grown stock culture of each of the specified microorganisms. Incubate the bacterial cultures at 30° to 35° for 18 to 24 hours, the culture of *C. albicans* at 20° to 25° for 48 hours, and the culture of *A. niger* at 20° to 25° for 1 week.

* Available from American Type Culture Collection, 12301 Parklawn Drive, Rockville, Md. 20852.

XIV. Xylose-Lysine-Desoxycholate Agar Medium

Xylose	3.5 g
l-Lysine	5.0 g
Lactose	7.5 g
Sucrose	7.5 g
Sodium Chloride	5.0 g
Yeast Extract	3.0 g
Phenol Red	80 mg
Agar	13.5 g
Sodium Desoxycholate	2.5 g
Sodium Thiosulfate	6.8 g
Ferric Ammonium Citrate	800 mg
Water	1000 ml

Final pH: 7.4 ± 0.2.

Heat the mixture of solids and water, with swirling, just to the boiling point. *Do not overheat or sterilize.* Transfer at once to a water bath maintained at about 50°, and pour into plates as soon as the medium has cooled.

XV. Bismuth Sulfite Agar Medium

Beef Extract	5.0 g
Pancreatic Digest of Casein	5.0 g
Peptic Digest of Animal Tissue	5.0 g
Dextrose	4.0 g
Sodium Phosphate	300 mg
Ferrous Sulfate	8.0 g
Bismuth Sulfite Indicator	20.0 g
Agar	25 mg
Brilliant Green	1000 ml
Water	

Final pH: 7.6 ± 0.2.

Heat the mixture of solids and water, with swirling, just to the boiling point. *Do not overheat or sterilize:* Transfer at once to a water bath maintained at about 50°, and pour into plates as soon as the medium has cooled.

XVI. Triple Sugar-Iron-Agar Medium

Pancreatic Digest of Casein	10.0 g
Peptic Digest of Animal Tissue	10.0 g
Lactose	10.0 g
Dextrose	10.0 g
Ferrous Ammonium Sulfate	1.0 g
Sodium Chloride	200 mg
Sodium Thiosulfate	5.0 g
Agar	200 mg
Phenol Red	13.0 g
Water	25 mg
	1000 ml

pH after sterilization: 7.3 ± 0.2.

XVII. MacConkey Agar Medium

Pancreatic Digest of Gelatin	17.0 g
Pancreatic Digest of Casein	1.5 g
Peptic Digest of Animal Tissue	1.5 g
Lactose	10.0 g
Bile Salts Mixture	1.5 g
Sodium Chloride	5.0 g
Agar	13.5 g
Neutral Red	30 mg
Crystal Violet	1.0 mg
Water	1000 ml

Boil the mixture of solids and water for 1 minute to effect solu-

pH after sterilization: 7.1 ± 0.2.

XVIII. Levine Eosin-Methylene Blue Agar Medium

Pancreatic Digest of Gelatin	10.0 g
Dibasic Potassium Phosphate	2.0 g
Agar	15.0 g
Lactose	10.0 g
Eosin Y	400 mg
Methylene Blue	65 mg
Water	1000 ml

Dissolve the pancreatic digest of gelatin, the dibasic potassium phosphate and the agar in the water, with warming, and allow to dissolve. Just prior to use, liquefy the gelled agar solution, add the remaining ingredients, as solutions, in the following amounts, and mix: for each 100 ml of the liquefied agar solution—5 ml of lactose solution (1 in 5), 2 ml of the eosin Y solution (1 in 50), and 2 ml of methylene blue solution (1 in 300). The finished medium may not be clear.

pH after sterilization: 7.1 ± 0.2.

Sampling

Provide separate 10-ml or 10-g specimens for each of the tests called for in the individual monograph.

Procedure

Prepare the specimen to be tested, by treatment that is appropriate to its physical characteristics and that does not alter the number and kind of microorganisms originally present, in order to obtain a solution or suspension of all or part of it in a form suitable for the test procedure(s) to be carried out.

For a solid that dissolves to an appreciable extent but not completely, reduce the substance to a moderately fine powder, suspend it in the vehicle specified, and proceed as directed under *Total Aerobic Microbial Count*, and under *Test for Staphylococcus and Pseudomonas* and *Test for Salmonella Species and Escherichia coli*.

For a fluid specimen that consists of a true solution, or a suspension in water or a hydroalcoholic vehicle containing less than 30 percent of alcohol, and for a solid that dissolves readily and practically completely in 90 ml of *pH 7.2 Phosphate Buffer* or the media specified, proceed as directed under *Total Aerobic Microbial Count*, and under *Test for Staphylococcus and Pseudomonas* and *Test for Salmonella Species and Escherichia coli*.

For water-immiscible fluids, ointments, creams, and waxes, prepare a suspension with the aid of a minimal quantity of a suitable, sterile emulsifying agent (such as one of the polysorbates), using a mechanical blender and warming to a temperature not exceeding 45°, if necessary, and proceed with the suspension as directed under *Total Aerobic Microbial Count*, and under *Test for Staphylococcus and Pseudomonas* and *Test for Salmonella Species and Escherichia coli*.

For a fluid specimen in aerosol form, chill the container in an alcohol–dry ice mixture for approximately 1 hour, cut open the container, allow it to reach room temperature, permit the propellant to escape, or warm to drive off the propellant if feasible, and transfer the quantity of test material required for the procedures specified in one of the two preceding paragraphs, as appropriate. Where 10.0 g or 10.0 ml of the specimen, whichever is applicable, cannot be

Table 1. Most Probable Total Count by Multiple-tube Method.

Observed Combinations of Numbers of Tubes Showing Growth in Each Set			
No. of mg (or ml) of Specimen per Tube			Most Probable Number of Microorganisms per g or per ml
100 (100 µl)	10 (10 µl)	1 (1 µl)	
3	3	3	>1100
3	3	2	1100
3	3	1	500
3	3	0	200
3	3	3	290
3	2	3	210
3	2	2	150
3	2	1	90
3	2	0	
3	1	3	160
3	1	2	120
3	1	1	70
3	1	0	40
3	0	3	95
3	0	2	60
3	0	1	40
3	0	0	23

Table 2. Morphologic Characteristics of *Staphylococcus aureus* on Selective Agar Media.

Selective Medium	Vogel-Johnson Agar Medium	Mannitol-Salt Agar Medium	Baird-Parker Agar Medium
Characteristic Colonial Morphology	Black surrounded by yellow zone	Yellow colonies with yellow zones	Black, shiny, surrounded by clear zones 2 to 5 mm
Gram Stain	Positive cocci (in clusters)	Positive cocci (in clusters)	Positive cocci (in clusters)

obtained from 10 containers in aerosol form, transfer the entire contents from 10 chilled containers to the culture medium, permit the propellant to escape, and proceed with the test on the residues. If the results of the test are inconclusive or doubtful, repeat the test with a specimen from 20 more containers.

Total Aerobic Microbial Count—For specimens that are sufficiently soluble or translucent to permit use of the *Plate Method*, use that method; otherwise, use the *Multiple-tube Method*. With a solid, or 10 ml, accurately measured, if the specimen is a liquid, in pH 7.2 Phosphate Buffer, Fluid Soybean-Casein Digest Medium, or Fluid Casein Digest–Soy Lecithin–Polysorbate 20 Medium to make 100 ml. For viscous specimens that cannot be pipeted at this initial 1:10 dilution, dilute the specimen until a suspension is obtained, i.e., 1:50 or 1:100, etc., that can be pipeted. Perform the test for absence of inhibitory (antimicrobial) properties as described under *Preparatory Testing* before the determination of *Total Aerobic Microbial Count*. Add the specimen to the medium not more than 1 hour after preparing the appropriate dilutions for isolation.

PLATE METHOD—Dilute further, if necessary, the fluid so that 1 ml will be expected to yield between 30 and 300 colonies. Pipet 1 ml of the final dilution onto each of two sterile Petri dishes. Promptly add to each dish 15 to 20 ml of Soybean-Casein Digest Agar Medium that previously has been melted and cooled to approximately 45°. Cover the Petri dishes, mix the sample with the agar by tilting or rotating the dishes, and allow the contents to solidify at room temperature. Invert the Petri dishes, and incubate for 48 to 72 hours. Following incubation, examine the plates for growth, count the number of colonies, and express the average for the two plates in terms of the number of microorganisms per g or per ml of specimen. If no microbial colonies are recovered from the dishes representing the initial 1:10 dilution of the specimen, express the results as "less than 10 microorganisms per g or per ml of specimen."

MULTIPLE-TUBE METHOD—Into each of fourteen test tubes of similar size place 9.0 ml of sterile Fluid Soybean-Casein Digest Medium. Arrange twelve of the tubes in four sets of three tubes each. Put aside one set of three tubes to serve as the controls. Into each of three tubes of one set ("100") and into a fourth tube (*A*) pipet 1 ml of the solution or suspension of the specimen, and mix. Into each tube of the third set ("1") pipet 1 ml from tube *A*; pipet 1 ml of its contents into the one remaining tube not included in a set, and mix. These two tubes contain 100 mg (or 100 µl) and 10 mg (or 10 µl) of the specimen, respectively. Into each tube of the second set ("10") of three tubes pipet 1 ml from tube *B*. Discard the unused contents of tubes *A* and *B*. Close well, and incubate all of the tubes. Following the incubation period, examine the tubes for growth: the three control tubes remain clear and the dilutions in the tubes containing the specimen, when interpreted by reference to Table 1, indicate the most probable number of organisms per g or per ml of specimen.

Test for *Staphylococcus aureus* and *Pseudomonas aeruginosa*—To the specimen add Fluid Soybean-Casein Digest Medium to make 100 ml, mix, and incubate. Examine the medium for growth, and if growth is present, use an inoculating loop to streak a portion of the medium on the surface of Vogel-Johnson Agar Medium (or Baird-Parker Agar Medium, or Mannitol-Salt Agar Medium) and of Cetrimide Agar Medium, each plated on Petri dishes. Cover and invert the dishes, and incubate. If, upon examination, none of the plates contains colonies having the characteristics listed in Tables 2 and 3 for the media used, the test specimen meets the requirements for freedom from *Staphylococcus aureus* and *Pseudomonas aeruginosa*.

COAGULASE TEST (FOR *Staphylococcus aureus*)—With the aid of an inoculating loop, transfer representative suspect colonies from the agar surfaces of the Vogel-Johnson Agar Medium (or Baird-Parker Agar Medium, or Mannitol-Salt Agar Medium) to individual tubes, each containing 0.5 ml of mammalian, preferably rabbit or horse, plasma with or without suitable additives. Incubate in a water bath at 37°, examining the tubes at 3 hours and subsequently at suitable intervals up to 24 hours. Test positive and negative controls simultaneously with the unknown specimens. If no coagulation in any degree is observed, the specimen meets the requirements of the test for absence of *Staphylococcus aureus*.

OXIDASE AND PIGMENT TESTS (FOR *Pseudomonas aeruginosa*)—With the aid of an inoculating loop, streak representative suspect colonies from the agar surface of Cetrimide Agar Medium on the agar surfaces of Pseudomonas Agar Medium for Detection of Fluorescin and Pseudomonas Agar Medium for Detection of Pyocyanin contained in Petri dishes. If numerous colonies are to be transferred, divide the surface of each plate into quadrants, each of which may be inoculated from a separate colony. Cover and invert the inoculated media, and incubate at 35 ± 2° for not less than three days. Examine the streaked surfaces under ultraviolet light. Examine the plates to determine whether colonies having the characteristics listed in Table 3 are present.

Confirm any suspect colonial growth on one or more of the media as *Pseudomonas aeruginosa* by means of the oxidase test. Upon the colonial growth place or transfer colonies to strips or disks of filter paper that previously has been impregnated with *N,N*-dimethyl-*p*-phenylenediamine dihydrochloride: if there is no development of a pink color, changing to purple, the specimen meets the requirements of the test for the absence of *Pseudomonas aeruginosa*. The presence of *Pseudomonas aeruginosa* may be confirmed by other suitable cultural and biochemical tests, if necessary.

Test for *Salmonella* Species and *Escherichia coli*—To the specimen, contained in a suitable vessel, add a volume of Fluid Lactose Medium to make 100 ml, and incubate. Examine the medium for growth, and if growth is present, mix by gently shaking. Pipet 1-ml portions into vessels containing, respectively, 10 ml of Fluid Selenite-Cystine Medium and Fluid Tetrathionate Medium, mix, and incubate for 12 to 24 hours. (Retain the remainder of the Fluid Lactose Medium.)

TEST FOR *Salmonella* SPECIES—By means of an inoculating loop, streak portions from both the selenite-cystine and tetrathionate media on the surface of Brilliant Green Agar Medium, Xylose-

Table 3. Morphologic Characteristics of *Pseudomonas aeruginosa* on Selective and Diagnostic Agar Media.

Medium	Cetrimide Agar Medium	Pseudomonas Agar Medium for Detection of Fluorescin	Pseudomonas Agar Medium for Detection of Pyocyanin
Characteristic Colonial Morphology	Generally greenish	Generally colorless to yellowish	Generally greenish
Fluorescence in Ultraviolet Light	Greenish	Yellowish	Blue
Oxidase Test	Positive	Positive	Positive
Gram Stain	Negative rods	Negative rods	Negative rods

Table 4. Morphologic Characteristics of *Salmonella* Species on Selective Agar Media.

Medium	Description of Colony
Brilliant Green Agar Medium	Small, transparent, colorless or pink to white opaque (frequently surrounded by pink to red zone)
Xylose-Lysine-Desoxycholate Agar Medium	Red, with or without black centers
Bismuth Sulfite Agar Medium	Black or green

Table 5. Morphologic Characteristics of *Escherichia coli* on MacConkey Agar Medium.

Characteristic Colonial Morphology	Brick-red; may have surrounding zone of precipitated bile
Gram Stain	Negative rods (cocco-bacilli)

Lysine-Desoxycholate Agar Medium, and Bismuth Sulfite Agar Medium contained in Petri dishes. Cover and invert the dishes, and incubate. Upon examination, if none of the colonies conforms to the description given in Table 4, the specimen meets the requirements of the test for absence of the genus *Salmonella*.

If colonies of Gram-negative rods matching the description in Table 4 are found, proceed with further identification by transferring representative suspect colonies individually, by means of an inoculating wire, to a butt-slant tube of Triple Sugar-Iron-Agar Medium by first streaking the surface of the slant and then stabbing the wire well beneath the surface. Incubate. If examination discloses no evidence of tubes having alkaline (red) slants and acid (yellow) butts (with or without concomitant blackening of the butt from hydrogen sulfide production), the specimen meets the requirements of the test for the absence of the genus *Salmonella*.*

TEST FOR *Escherichia coli*—By means of an inoculating loop, streak a portion from the remaining Fluid Lactose Medium on the surface of MacConkey Agar Medium. Cover and invert the dishes, and incubate. Upon examination, if none of the colonies conforms to the description given in Table 5 for this medium, the specimen meets the requirements of the test for absence of *Escherichia coli*.

If colonies matching the description in Table 5 are found, proceed with further identification by transferring the suspect colonies individually, by means of an inoculating loop, to the surface of Levine Eosin-Methylene Blue Agar Medium, plated on Petri dishes. If numerous colonies are to be transferred, divide the surface of each plate into quadrants, each of which may be seeded from a separate colony. Cover and invert the plates, and incubate. Upon examination, if none of the colonies exhibits both a characteristic metallic sheen under reflected light and a blue-black appearance under transmitted light, the specimen meets the requirements of the test for the absence of *Escherichia coli*. The presence of *Escherichia coli* may be confirmed by further suitable cultural and biochemical tests.

RETEST—For the purpose of confirming a doubtful result by any of the procedures outlined in the foregoing tests following their application to a 10.0-g specimen, a retest on a 25-g specimen of the product may be conducted. Proceed as directed under *Procedure*, but make allowance for the larger specimen size.

⟨71⟩ STERILITY TESTS[1]

The sterility tests presented herein are suitable for revealing the presence of viable forms of bacteria, fungi, and yeasts in or on Pharmacopeial articles. Alternative procedures or procedural details may be employed to demonstrate that an article is sterile, provided the results obtained are at least of equivalent reliability. (See *Procedures* under *Tests and Assays* in the *General Notices*.) Where a difference appears, or in the event of a dispute, when evidence of microbial contamination is obtained by the procedure given in this Pharmacopeia, the result so obtained is conclusive of failure of the article to meet the requirements of the test.

Adventitious microbial growth that is transmitted to an article or to inoculated test culture media from the environment during the course of a sterility test invalidates the results of the test. Hence, it is necessary to demonstrate that the proper precautions have been taken to exclude extraneous microorganisms throughout the test period.

Where a sterility test is applied to discrete units drawn from a group of similar units, the results obtained, if negative, indicate that the probability of the presence of contaminated units in the untested portion is below a level detectable by the sampling plan employed. No sampling plan for applying sterility tests to a specified proportion of discrete units selected from a sterilization load is capable of demonstrating with complete assurance that all of the untested units are in fact sterile. A further review of validation of sterilization is presented in the informational chapter on *Sterilization* ⟨1211⟩.

The sterility testing of human biologics and antibiotics is conducted by specific procedures set forth in the regulations applicable to their manufacture or distribution (see *Antibiotics* ⟨1011⟩ and *Biologics* ⟨1041⟩). Veterinary biologics are tested for sterility or microbiological attributes as directed in the regulations applicable to those products (9 CFR, 113.26).

Media

Media for the tests may be prepared as described below, or dehydrated mixtures yielding similar formulations may be used provided that, when reconstituted as directed by the manufacturer or distributor, they have growth-promoting properties equal or superior to those obtained from the formulas given herein.

I. Fluid Thioglycollate Medium

L-Cystine	0.5 g
Sodium Chloride	2.5 g
Dextrose ($C_6H_{12}O_6 \cdot H_2O$)	5.5 g
Agar, granulated (moisture content not in excess of 15%)	0.75 g
Yeast Extract (water-soluble)	5.0 g
Pancreatic Digest of Casein	15.0 g
Sodium Thioglycollate or Thioglycollic Acid	0.5 g
Resazurin Sodium Solution (1 in 1000), freshly prepared	0.3 ml
Water	1.0 ml
	1000 ml

pH after sterilization: 7.1 ± 0.2.

Mix, in the order named, the L-cystine, sodium chloride, dextrose, agar, water-soluble yeast extract, and pancreatic digest of casein, in a mortar, with thorough grinding. Stir in a small quantity of heated water, transfer to a suitable container, with repeated washing of the mortar add the remainder of the 1000 ml of water, and heat until solution is effected. Dissolve the sodium thioglycollate or thioglycollic acid in the solution and, if necessary, adjust the solution with sodium hydroxide TS so that, after sterilization, it will have a pH of 7.1 ± 0.2. If filtration is necessary, heat the solution again without boiling, and filter while hot through moistened filter paper. Add the resazurin sodium solution, mix, and place the medium in suitable vessels, which provide a ratio of surface to depth of medium such that not more than the upper half of the medium has undergone a color change indicative of oxygen uptake at the end of the incubation period. Sterilize in an autoclave (see *Steam Sterilization* under *Sterilization* ⟨1211⟩). Do not use this medium if it is evaporated to an extent affecting its fluidity. If more than the upper one-third has acquired a pink color, the medium may be restored once by heating on a steam bath or in free-flowing steam until the pink color disappears. When ready for use, approximately the upper one-tenth of the medium should have a pink color.

Use Fluid Thioglycollate Medium by incubating it under aerobic

[1] Additional confirmatory evidence may be obtained by use of procedures set forth in *Official Methods of Analysis of the AOAC*, 12th ed (1975), sections 46.013-46.026.

* All temperatures herein specified are in Celsius (centigrade) degrees and, with respect to autoclaves, generally mean

II. Alternative Thioglycollate Medium for Devices Having Tubes with Small Lumina

L-Cystine	0.5 g
Sodium Chloride	2.5 g
Dextrose ($C_6H_{12}O_6 . H_2O$)	5.5 g
Yeast Extract (water-soluble)	5.0 g
Pancreatic Digest of Casein	15.0 g
Sodium Thioglycollate	0.5 g
or Thioglycollic Acid	0.3 ml
Water	1000 ml

pH after sterilization: 7.1 ± 0.2.

Heat the ingredients in a suitable container until solution is effected. Mix, and, if necessary, adjust the solution with sodium hydroxide TS so that, after sterilization, it will have a pH of 7.1 ± 0.2. Filter, if necessary, place in suitable vessels, and sterilize in an autoclave (see *Steam Sterilization* under *Sterilization* ⟨1211⟩). The medium is freshly prepared or heated in a steam bath and allowed to cool just prior to use. Do not reheat.

Use Alternative Thioglycollate Medium in a manner that will ensure anaerobic conditions for the duration of the incubation period.

III. Soybean-Casein Digest Medium

Pancreatic Digest of Casein	17.0 g
Papaic Digest of Soybean Meal	3.0 g
Sodium Chloride	5.0 g
Dibasic Potassium Phosphate	2.5 g
Dextrose ($C_6H_{12}O_6 . H_2O$)	2.5 g
Water	1000 ml

pH after sterilization: 7.3 ± 0.2.

Dissolve the solids in the water, warming slightly to effect solution. Cool the solution to room temperature, and adjust with sodium hydroxide TS, if necessary, to obtain a pH of 7.3 ± 0.2 after sterilization. Filter, if necessary, and dispense into suitable vessels. Sterilize in an autoclave (see *Steam Sterilization* under *Sterilization* ⟨1211⟩).

Use Soybean-Casein Digest Medium by incubating it under aerobic conditions.

Growth Promotion Test

Test each autoclaved lot of medium for its growth-promoting properties, in the following manner.

Inoculate duplicate test containers of each medium with less than 100 of the microorganisms listed in the accompanying table, and incubate according to the conditions specified for it.

The test media are satisfactory if evidence of growth appears within 7 days. The tests may be conducted simultaneously with those of the test media for sterility test purposes, provided, however, that the sterility test is considered invalid if the test medium shows no growth response.

Confirm the sterility of each lot of medium by incubation of representative containers, at the temperature and for the length of time specified in the test.

If freshly prepared media are not used within 2 days, store them in the dark, preferably at 2° to 25°. Finished media may be stored in sealed containers for more than 10 days, provided that they are tested weekly for growth promotion. If stored in suitable sealed containers, the media may be used for not more than 1 year, provided that they are tested for growth promotion every three months.

Medium	Test Microorganisms*	Incubation Temperature (°)
Fluid Thioglycollate	(1) *Bacillus subtilis* (ATCC No. 6633)†	30 to 35
	(2) *Candida albicans* (ATCC No. 10231)‡	30 to 35
	(3) *Bacteroides vulgatus* (ATCC No. 8482)‡	30 to 35
Alternative Thioglycollate	(1) *Bacteroides vulgatus* (ATCC No. 8482)‡	30 to 35
Soybean-Casein Digest	(1) *Bacillus subtilis* (ATCC No. 6633)†	20 to 25
	(2) *Candida albicans* (ATCC No. 10231)	20 to 25

*Available from the American Type Culture Collection, 12301 Parklawn Drive, Rockville, Md. 20852.

†A spore-forming organism is not desired, use *Micrococcus luteus* (ATCC No. 9341) at the incubation temperatures indicated in the table.

‡A spore-forming organism is desired, use *Clostridium sporogenes* (ATCC No. 11437) at the incubation temperature indicated in the table.

Bacteriostasis and Fungistasis

Before initiating direct transfer sterility tests on an article, obtain background data on the level of bacteriostatic and fungistatic activity by the following procedures. Prepare dilute cultures of bacteria and fungi from at least the microorganisms cited under *Growth Promotion Test*. Inoculate the sterility test media with less than 100 of the microorganisms, employing volumes of medium listed in the table of "Quantities for Liquid Articles," under *Selection of Test Specimens and Incubation*. Add the specified portion of article to half of a suitable number of the containers already containing the inoculum and culture medium. Incubate the containers at appropriate temperatures and under proper conditions for not less than 7 days.

If growth of the test organisms comparable to that in the control vessels occurs in the article-medium mixtures, use the amounts of article and medium regularly specified in the table of "Quantities for Liquid Articles," under *Selection of Test Specimens and Incubation*.

If the article is bacteriostatic and/or fungistatic when tested as described above, use a suitable sterile inactivating agent, if available. Suitability of such an inactivating agent is determined as in the test described below. If an inactivating agent is not available, establish, as described below, suitable amounts of article and medium to be used.

Repeat the tests set forth above, using the specified amount of article and larger volumes of the medium to determine the ratio of article to medium in which growth of the test organisms is not affected.

If the specified amount of article is bacteriostatic or fungistatic in 250 ml of the medium, decrease the amount of the article to find the maximum amount that does not materially affect the growth of the test organism in 250 ml of the medium. For liquids and suspensions, if this amount is less than 1 ml, increase the quantity of medium so that the 1 ml is sufficiently diluted to prevent inhibition of growth. For solids that are not readily soluble or dispersible, if the amount is less than 50 mg, increase the quantity of medium so that the 50 mg of the article is sufficiently diluted to prevent inhibition of growth. In either case, use the amounts of the article and medium established in this ratio for routine testing. Where applicable, sterility may be tested as described under *Test Procedures using Membrane Filtration*.

General Procedure

Because of diversity in the nature of articles to be tested and other factors affecting the conduct of the sterility test, it is important to observe the following considerations in performing sterility tests.

OPENING CONTAINERS

Cleanse the exterior surfaces of ampuls and closures of vials and bottles with a suitable decontaminating agent, and gain access to the contents in a suitable aseptic manner. If the vial contents are packaged under vacuum, admit sterile air by means of a suitable sterile device, such as a needle attached to a syringe barrel filled with nonabsorbent cotton.

For purified cotton, gauze, surgical dressings, and related Pharmacopeial articles, open the package or container aseptically.

SELECTION OF TEST SPECIMENS AND INCUBATION

The quantity of information provided by sterility testing is related to the number of units tested. Unless otherwise directed in the individual monograph or in a section of this chapter, test 20 units of the article with each medium.[2]

For liquid articles from each unit, use not less than the volumes of article and medium specified in the table of "Quantities for Liquid Articles," in this section. If the contents are of sufficient quantity, they may be divided so that portions are added to the two specified media.

For articles in which only the lumen must be sterile, flush the lumen with a suitable quantity of medium to yield a recovery of not less than 15 ml of medium. Unless otherwise directed in the individual monograph or in a section of this chapter, incubate the test mixture for 14 days with Fluid Thioglycollate Medium or Alternative Thioglycollate Medium, where so indicated, at 30° to 35°, and with Soybean-Casein Digest Medium at 20° to 25°.

Test Procedures for Direct Transfer to Test Media

LIQUIDS

Remove liquids from test containers with a sterile pipet or with a sterile syringe and needle. Aseptically transfer the specified volume of the material from each test container to a vessel of culture medium. Mix the liquid with the medium, but do not aerate excessively. Incubate in the specified media for not less than 14 days.

Where the material being tested renders the medium turbid, so that the presence or absence of microbial growth cannot be determined readily by visual examination, transfer suitable portions of the medium to fresh vessels of the same medium between the third and seventh days after the test is started. Continue incubation of the original and of the transfer vessels for not less than 7 additional days after the transfer and for a total of not less than 14 days.

OINTMENTS AND OILS INSOLUBLE IN ISOPROPYL MYRISTATE

Select 20 containers, assign them to 2 groups of 10 containers, and treat each group as follows. Aseptically transfer 100 mg from each of the 10 containers to a flask containing 100 ml of a sterile, aqueous vehicle capable of dispersing the test material homogeneously throughout the fluid mixture. [NOTE—The choice of dispersing agent incorporated in the aqueous vehicle may differ according to the nature of the ointment or oil. Before use, test the dispersing agent to ascertain that in the concentration used it has no significant antimicrobial effects during the time interval for all transfers.] Mix 10 ml of the fluid mixture so obtained with 80 ml of medium, and proceed as directed under *Liquids*.

SOLIDS

Transfer a quantity of the product in the form of a dry solid (or of a solution or a suspension of the product prepared by adding sterile diluent to the immediate container), corresponding to not less than 300 mg from each container being tested, or the entire contents if less than 300 mg, to not less than 40 ml of Fluid Thioglycollate Medium and to not less than 40 ml of Soybean-Casein Digest Medium, respectively, and mix, the number of containers and the conditions of incubation being the same as for liquids. Proceed as directed under *Liquids*, beginning with "Where the material."

PURIFIED COTTON, GAUZE, SURGICAL DRESSINGS, AND RELATED ARTICLES

From each package of cotton, rolled gauze, or gauze bandage being tested, remove with sterile instruments two or more portions of 100 mg to 500 mg each from the innermost part of the sample. From individually packaged single-use materials such as gauze pads, remove a single portion of 250 mg to 500 mg or the entire article in the case of small, i.e., 25- × 75-mm or smaller, adhesive absorbent bandages.

Aseptically transfer these portions of the article to the specified number of containers of appropriate media.

SUTURES

Place the container in a suitable antimicrobial solution containing crystal violet or another suitable dye, for not less than 3 hours. Remove with sterile forceps, and if the container shows no evidence of leakage, hold under aseptic conditions prior to testing. Open the containers aseptically, and with sterile instruments transfer sutures to containers of appropriate media.

STERILIZED DEVICES

The following considerations apply to sterilized devices manufactured in lots, each consisting of a number of units. Special considerations apply to sterile devices manufactured in small lots or in individual units where the self-destructive nature of the Sterility Test renders the conventional Sterility Test impracticable. For these articles appropriate and acceptable modifications to the Sterility Test must be made.

For articles of such size and shape as to permit complete immersion in not more than 1000 ml of culture medium, test the intact article, using the appropriate media, and incubate as directed under *General Procedure*.

For devices having hollow tubes, such as transfusion or infusion assemblies, or where the size of an item makes immersion impracticable and only the fluid pathway must be sterile, flush the lumen of each of 20 units with a sufficient quantity of Fluid Thioglycollate Medium and the lumen of each of 20 units with a sufficient quantity

Quantities for Liquid Articles

Container content (ml)	Minimum volume taken from each container for each medium	Minimum Volume of Each Medium: Used for direct transfer of volume taken from each container (ml)	Minimum Volume of Each Medium: Used for total volume taken from all containers for membrane filtration (ml)	No. of containers per medium
Less than 10	1 ml, or entire contents if less than 1 ml	15	100	20
10 to less than 50	5 ml	40	100	20
50 to less than 100	10 ml	80	100	10
100 up to 500	Entire contents	—	100	10
Over 500	500 ml	—		

[2] Sterility tests are applied to individual discrete units or to composites of such units. The number of units specified is chosen only for practical considerations of the required laboratory manipulations in performing the referee test. As previously noted in the introductory paragraphs, results obtained in examining a discrete unit or units for sterility cannot be extrapolated with complete certainty to characterize the sterility of the untested portion of the lot.

...Soybean-Casein Digest Medium to yield a recovery of not less ...than 0.5 ml of each medium, and incubate with not less than 100 ml ...of each of the two media as directed under *General Procedure*. For ...devices in which the lumen is so small that Fluid Thioglycollate ...Medium will not pass through, substitute Alternative Thioglycollate ...Medium for Fluid Thioglycollate Medium, and incubate that ...medium anaerobically.

Where the entire intact article cannot be tested for sterility because of its size and shape, by immersion in not more than 1000 ml of a sterile medium expose that portion of the article most difficult to sterilize, and test that portion, or where practicable remove two or more portions each from the innermost portion of the article. Aseptically transfer these portions of the article to the specified number of vessels of appropriate media in a volume of not more than 100 ml, and incubate as directed under *General Procedure*.

Where the presence of the test specimen in the medium interferes with the test because of bacteriostatic or fungistatic action, rinse the article thoroughly with a minimal amount of rinse fluid (see *Diluting and Rinsing Fluids* under *Test Procedures using Membrane Filtration*). Recover the rinse fluid, and test as directed for articles under *Test Procedures using Membrane Filtration*.

PREFILLED DISPOSABLE SYRINGES

Sterility testing of prefilled disposable syringes is to be performed using the same aseptic techniques as exercised when testing sterile products contained in ampuls or vials. A Direct Transfer or a Membrane Filtration technique may be employed for the product after a Bacteriostasis and Fungistasis test has been established. The product should be flushed through the lumen of needles for attached or activated needle-type syringes. For detached needle-type syringes, it may be preferable to flush sterile media through the lumen of the needle and subject the media to a sterility test. In addition, special attention is to be directed toward demonstrating that the outside of the needle (that portion that enters the patient) is sterile.

PETROLATUM GAUZE

Prepare Fluid Thioglycollate Medium as directed except to use 0.5 g of agar and to add 5.0 g of gelatin for each liter of medium, and test as described under *Growth Promotion Test*.

Place 300 ml of medium in suitable wide-mouth containers of about 500-ml capacity. Loosely close each jar with an aluminum closure without a liner but with a rubber ring gasket fitted to the inside circumference of the lid, and secure with a muslin cover during sterilization and until ready to use. Sterilize in an autoclave (see *Steam Sterilization* under *Sterilization* (1211)).

To the medium warmed to 52° transfer aseptically the entire contents of a single package of the Petrolatum Gauze to be tested. Close tightly, and shake each container in a reciprocating shaker for 10 minutes. Cool the container in a slanting position until the petrolatum forms a solid seal over the surface of the medium. Then break the petrolatum seal by a single quick shake. Incubate at 20° to 35° for not less than 7 days, then shake in a reciprocating shaker for 10 minutes. Transfer aseptically 0.5 ml of the product-medium mixture to 15 ml of culture medium. Incubate at 30° to 35° for not less than 7 days.

Test Procedures Using Membrane Filtration

The sterility testing of Pharmacopeial articles should be performed when feasible by membrane filtration of the test specimens. This procedure is applicable in the sterility testing of non-bacteriostatic or non-fungistatic liquids or soluble powders, and is particularly appropriate where the article is an oil, an ointment, or a solid that can be put into solution with non-bacteriostatic or non-fungistatic diluting fluids. The membrane filtration technique is also appropriate also in the sterility testing of liquids and soluble articles that possess inherent bacteriostatic or fungistatic properties. Certain devices also may be appropriately tested for sterility under the critical pathways by the membrane filtration technique. The manipulations additional to those employed in conducting a sterility test by direct transfer may be a potential source of extraneous contamination. The frequent use of negative controls is highly recommended.

Apparatus—A suitable unit consists of a closed reservoir and a receptacle between which a properly supported membrane or membranes of appropriate porosity is (are) placed. A membrane generally suitable for sterility testing has a nominal porosity of 0.45 ± 0.02 μm, a diameter of approximately 47 mm, and a flow-rate of 55 to 75 ml of water per minute at a pressure of 70 cm of mercury. The entire unit may be assembled and sterilized with the membrane(s) in place prior to use in the test, or the membranes may be sterilized separately by steam under pressure, or by any method that yields proper performance.

Where the article to be tested is an oil, sterilize the membrane separately, and after thorough drying, assemble the unit, using aseptic precautions.

Diluting and Rinsing Fluids—

FLUID A—Dissolve 1 g of peptic digest of animal tissue (see *Reagents, Indicators, and Reagent Specifications* in the section, *Reagents, Indicators, and Solutions*) in water to make 1 liter, filter or centrifuge to clarify, adjust to a pH of 7.1 ± 0.2, dispense into containers in 100-ml quantities, and sterilize in an autoclave (see *Steam Sterilization* under *Sterilization* (1211)).

FLUID D—If the test specimen contains lecithin or oil, use *Fluid A* to each liter of which has been added 1 ml of polysorbate 80, adjust to pH 7.1 ± 0.2, dispense into flasks, and sterilize in an autoclave (see *Steam Sterilization* under *Sterilization* (1211)).

NOTE—A sterile fluid must not have antibacterial or antifungal properties if it is to be considered suitable for dissolving, diluting, or rinsing an article under test for sterility.

LIQUIDS MISCIBLE WITH AQUEOUS VEHICLES (LESS THAN 100 ml PER CONTAINER)

Aseptically transfer the volumes required for both media, as indicated in *Quantities for Liquid Articles* under *Selection of Test Specimens and Incubation*, from each of 20 containers (40 containers, if each one does not contain sufficient volume for both media) either directly into one or two separate membrane filter funnels or to separate sterile pooling vessels prior to transfer. The required volumes from not less than 20 containers are thus represented by the membrane, or membrane half, transferred to each medium. Immediately pass each specimen through the filter with the aid of vacuum or a pressure pump.

One or two membranes may be used for the entire number of containers prescribed. If the product is bacteriostatic or fungistatic, rinse the membrane(s) with three 100-ml portions of *Fluid A*. Aseptically remove the membrane(s) from the holder, cut the membrane in half, if only one is used, immerse the membrane, or one-half of the membrane, in 100 ml of Soybean-Casein Digest Medium, and incubate at 20° to 25° for not less than 7 days. Similarly, immerse the other membrane, or other half of the membrane, in 100 ml of Fluid Thioglycollate Medium, and incubate at 30° to 35° for not less than 7 days.

LIQUIDS MISCIBLE WITH AQUEOUS VEHICLES (100 ml OR MORE PER CONTAINER)

If the volume of liquid in the article is 500 ml or less, aseptically transfer the entire contents of not less than 10 containers through each of two filter assemblies, or not less than 20 containers at one filter assembly is used. If the volume of the liquid in the article is more than 500 ml, aseptically transfer not less than 500 ml from each of not less than 10 containers through each of two filter assemblies, or not less than 20 containers if one filter assembly is used. Treat the test membrane(s) as directed under *Liquids Miscible with Aqueous Vehicles (Less than 100 ml per Container)*, beginning with "One or two membranes may be used."

In some cases, where the liquid is highly viscous and not readily filterable through one or two membranes, more than two filter assemblies may be needed. On such cases, half the number of membranes used are incubated in each medium, provided that the volumes and requirements for numbers of containers per medium are complied with.

LIQUIDS IMMISCIBLE WITH AQUEOUS VEHICLES (LESS THAN 100 ml PER CONTAINER)

Using the contents of not less than 20 containers (40 containers, if each one does not contain sufficient volume for both media), aseptically transfer the volumes required for both media, as indicated in *Quantities for Liquid Articles* under *Selection of Test Specimens and Incubation*, either directly into one or two separate membrane filter funnels or to separate sterile pooling vessels prior to transfer. The required volumes from not less than 20 containers are thus represented by the membrane, or membrane half, trans-

ferred to each medium. Immediately pass each specimen through the filter with the aid of vacuum or a pressure pump.

If the substance is a viscous liquid or suspension not adaptable to rapid filtration, aseptically add a sufficient quantity of diluting fluid to the pooled specimen to increase the flow rate.

If the liquid under test has inherent bacteriostatic properties or contains a preservative, wash the filter with from one to three 100-ml portions of *Fluid A*. If the substance under test contains lecithin or oil, substitute *Fluid D* for *Fluid A*.

Upon completion of the filtration, transfer one membrane (if two are used) or approximately one-half of the membrane (if only one is used) aseptically to 100 ml of Soybean-Casein Digest Medium, and incubate at 20° to 25° for not less than 7 days. Similarly, proceed with 100 ml of Fluid Thioglycollate Medium and incubate at 30° to 35° for not less than 7 days.

OINTMENT AND OILS SOLUBLE IN ISOPROPYL MYRISTATE

Dissolve not less than 100 mg from each of not less than 20 containers (40 containers, if each one does not contain sufficient volume for both media) in at least 100 ml of isopropyl myristate at pH 5.5 or greater, which previously has been rendered sterile by filtration through a 0.22-μm membrane filter. [NOTE—Warm the sterilized solvent, and if necessary the test material, to 47° just prior to use.] Aseptically transfer the mixture into one or two membrane filter funnels. Immediately pass each specimen through the filter with the aid of vacuum or a pressure pump. Swirl the flask to dissolve the ointment or oil. Filter the dissolved ointment promptly following dissolution. Keep filter membrane(s) covered with liquid throughout the filtration for maximum efficiency of the filter.

Following filtration of the specimen, wash the membrane(s) with two 200-ml portions of *Fluid D*, then wash with 100 ml of *Fluid A*. Treat the test membrane(s) as directed under *Liquids Miscible with Aqueous Vehicles (Less than 100 ml per Container)*, beginning with "Aseptically remove the membrane(s)," except to provide that the sterility test medium to be used contains 1 g of polysorbate 80 per liter.

If the substance under test contains petrolatum, use a special rinse fluid of the following composition:

Peptic Digest of Animal Tissue (see *Reagent Specifications* in the section, *Reagents, Indicators, and Solutions*)	5.0 g
Beef Extract	3.0 g
Polysorbate 80	10.0 g
Water	1000 ml

pH after sterilization: 6.9 ± 0.2.

Sterilize in an autoclave (see *Steam Sterilization* under *Sterilization* ⟨211⟩).

Moisten the membrane(s) with approximately 200 μl of the rinse medium before the filtration operation begins, and keep the membrane(s) covered with liquid throughout the filtration operation for maximum efficiency of the filter.

Following filtration of the specimen, wash the membrane(s) with three 100-ml portions of the rinse medium. Treat the test membrane(s) as directed above.

NOTE—For ointments and oils that are insoluble in isopropyl myristate, proceed as directed for *Ointments and Oils Insoluble in Isopropyl Myristate* under *Test Procedures for Direct Transfer to Test Media*.

NON-FILTERABLE SOLIDS

The sterility testing of these articles by membrane filtration is considered inadvisable unless it can be demonstrated that filter blockage does not occur. Proceed as directed for *Solids* under *Test Procedures for Direct Transfer to Test Media*.

DEVICES

Devices that are required to contain sterile pathways may be tested for sterility by the membrane filtration technique as follows:

Aseptically pass a sufficient volume of *Fluid D* through each of not less than 20 devices so that not less than 100 ml is recovered from each device. Collect the fluids in aseptic containers, and filter the entire volume collected through membrane filter funnel(s) as described under *Liquids Miscible with Aqueous Vehicles (Less than 100 ml per Container)*, beginning with "One or two membranes may be used."

Where the devices are large, and lot sizes are small, test an appropriate number of units as described for similar cases under *Test Procedures for Direct Transfer to Test Media*.

Observation and Interpretation of Sterility Test Results

At intervals during the incubation period and at its conclusion, examine the contents of all of the vessels for macroscopic evidence of microbial growth, such as the development of turbidity. If no evidence of growth is found, the material tested meets the requirements of the test for *Sterility*. If evidence of microbial growth is found, the material tested fails to meet the requirements of the test for *Sterility*, unless it can be demonstrated by retests or by other means that the test was invalid for causes unrelated to the article.

In view of the possibility that microbial growth observed in the test was due to inadequate aseptic sampling and testing technique rather than to intrinsic contamination of the article, the following retests are permitted.

FIRST RETEST

The number of specimens selected, the volumes to be tested, and the media are the same as those indicated for the original *Sterility Test*. If no evidence of microbial growth is found, the material tested meets the requirements of the test for *Sterility*. If microbial growth appears in this *First Retest*, isolate and characterize the microbial contaminant(s) of the *First Retest* and compare to the contaminant(s) of the original *Sterility Test*. If the contaminant(s) cannot be differentiated readily, the material tested fails to meet the requirements of the test for *Sterility*. If the contaminant(s) can be differentiated readily, a *Second Retest* may be performed.

SECOND RETEST

The number of specimens selected is double the number tested in the original *Sterility Test* and in the *First Retest*. The volumes tested from each specimen and the media are the same as those indicated for the original *Sterility Test* and the *First Retest*.

If no evidence of microbial growth is found, the material tested meets the requirements of the test for *Sterility*. If growth appears in this *Second Retest*, the material tested fails to meet the requirements of the test for *Sterility*.

Biological Tests and Assays

⟨81⟩ ANTIBIOTICS—MICROBIAL ASSAYS

The activity (potency) of antibiotics may be demonstrated under suitable conditions by their inhibitory effect on microorganisms. A reduction in antimicrobial activity also will reveal subtle changes not demonstrable by chemical methods. Accordingly, microbiological assays remain generally the standard for resolving doubt with respect to possible loss of activity. The regulations of the federal Food and Drug Administration contain detailed procedures for the testing of all forms of antibiotics as a part of its procedure for granting batch certification of all antibiotics. The general statement given here summarizes these procedures for the antibiotics recognized in this Pharmacopeia for which microbiological assay remains the definitive method.

Two general methods are employed, the cylinder-plate or "plate" assay and the turbidimetric or "tube" assay. The first depends upon diffusion of the antibiotic from a vertical cylinder through a solidified agar layer in a Petri dish or plate to an extent such that growth of the added microorganism is prevented entirely in a circular area or "zone" around the cylinder containing a solution of the antibiotic. The turbidimetric method depends upon the inhibition of growth

the 6 cylinders on each plate with dilutions of antibiotic containing the test levels specified below, incubate the plates at 32° to 35°, or at the temperature specified below for the individual case, for 16 to 18 hours, remove the cylinders, and measure and record the diameter of each zone of growth inhibition to the nearest 0.1 mm. Incubate the plates at 30° for Amphotericin B, Nystatin, and Rifampin. Incubate at 35° for Novobiocin. Incubate at 37° for Carbenicillin, Clindamycin, Colistimethate Sodium, Colistin, Dactinomycin, Dihydrostreptomycin, Gentamicin, Kanamycin B, Mitomycin, Paromomycin, Polymyxin B, Ticarcillin, and Vancomycin.

For the 1-level assay with a standard curve, prepare dilutions representing 5 test levels of the Standard (S_1 to S_5) and a single test level of the Unknown U_3 corresponding to S_3 of the standard curve, as defined under *Preparation of the Standard* and *Preparation of the Sample*. For deriving the standard curve, fill alternate cylinders on each of 3 plates with the median test dilution (S_3) of the Standard and each of the remaining 9 cylinders with one of the other four dilutions of the Standard. Repeat the process for the other three dilutions of the Standard. For each Unknown, fill alternate cylinders on each of 3 plates with the median test dilution of the Standard (S_3), and the remaining 9 cylinders with the corresponding test dilution (U_3) of the Unknown.

TURBIDIMETRIC METHOD

On the day of the assay, prepare the necessary doses by dilution of stock solutions of the Standard and of each Unknown as defined under *Preparation of the Standard* and *Preparation of the Sample*. Add 1 ml of each dose to each of 3 prepared test tubes, and place the 3 replicate tubes in a position selected at random, in 1 or more tube racks. Include similarly in each rack 1 or 2 control tubes containing 1 ml of the test diluent (see Table 4) but no antibiotic. Upon completion of the three sets or racks of test solutions, add 9.0 ml of inoculum to each tube in each rack in turn, and place the completed rack immediately in an incubator or a water bath maintained at 37° ; except for Candicidin (incubate at 28°), for 2 to 3 hours. After incubation add 0.5 ml of dilute formaldehyde to each tube, taking one rack at a time, and read its transmittance or absorbance in a suitable spectrophotometer fitted with a 530-nm filter.

For the 1-level assay with a standard curve, prepare dilutions representing 5 test levels of the Standard (S_1 to S_5) and a single test level (U_3) of each of up to 20 Unknowns corresponding to S_3 of the Standard. Prepare also an extra S_3 as a test of growth. Add 1 ml of each test dilution, except for Gramicidin (use 0.1 ml) to 3 tubes and 1 ml of antibiotic-free diluent to 6 tubes as controls. Distribute one complete set, including 2 tubes of controls, to 1 or more tube racks, intermingling them at random. Add 9.0 ml of inoculum, incubate, add 0.5 ml of dilute formaldehyde, and complete the assay as directed above. Determine the exact duration of incubation by observation of growth in the reference concentration (median dose) of the dilutions of the standard (S_3).

Calculation

To calculate the potency from the data obtained either by the cylinder-plate or by the turbidimetric method, proceed in each case as directed under *Potencies Interpolated from a Standard Curve* (see (111)), using a log transformation, straight-line method with a least squares fitting procedure, and a test for linearity. Where a number of assays of the same material are made with the same standard curve, calculate the coefficient of variation of results of all of the assays of the material. Where more than one assay is made of the same material with different standard curves, average the two or more values of the log potency. The potency is the antilog of the combined log potencies.

⟨85⟩ BACTERIAL ENDOTOXINS TEST

This chapter provides a test for estimating the concentration of bacterial endotoxins that may be present in or on the sample of the article(s) to which the test is applied. These endotoxins are lipopolysaccharides that are pyrogens. The reagent employed for detecting and measuring such endotoxins is Limulus Amebocyte Lysate (LAL) obtained from aqueous extracts of the circulating amebocytes of the horseshoe crab, *Limulus polyphemus*. In the presence of minute concentrations of endotoxins (of the order of pg/ml in the case of potent endotoxin preparations made from *Escherichia coli*), LAL reagent exhibits a protein coagulation reaction (gel, turbidity or precipitate) under prescribed in-vitro test conditions and in the absence of interfering substances. Biochemical studies indicate that, in addition to endotoxin, three other factors are necessary to produce the protein coagulation reaction: a proclotting enzyme, clottable protein (coagulogen), and certain divalent cations. The constituted LAL reagent provides these factors.

In preparing for and applying the test, observe precautions in handling the specimens in order to avoid gross microbial contamination, and treat any containers or utensils employed to destroy extraneous endotoxins that may be present on their surfaces, such as by heating in an oven at 250° or above for sufficient time to render their surfaces negative to the test, but not less than 30 minutes. Where the test is conducted as a limit test, the specimen is determined to be positive or negative to the test judged against some pre-established endotoxin concentration. Positive and negative controls are essential.

For validating the test for an article, or for special purposes where so specified, testing of specimens is conducted quantitatively to determine response end-points. Usually graded strengths of the specimen and endotoxin control are made by multifold dilutions. Dilutions selected so that they correspond to a geometric series in which each step is greater than the next lower by a constant ratio, or to an arithmetic series with constant intervals in concentrations are not precluded. Do not store diluted endotoxin, because of loss of activity by adsorption. As a general rule and in the absence of supporting data to the contrary, negative and positive controls are incorporated in the test. Replication within dilution series is essential for assessing the error and confidence in the results obtained and for computing the geometric means of end-point values.

Reference Standard and Control Standard Endotoxins

The reference standard endotoxin (RSE) is the U.S. Reference Endotoxin designated EC-2 by the Bureau of Biologics of the federal Food and Drug Administration. It has a defined potency of 5.0 Endotoxin Units per ng. A control standard endotoxin (CSE) is an endotoxin preparation other than the RSE that has been standardized against the RSE.

Preparatory Testing

The validity of test results for bacterial endotoxins requires an adequate demonstration that specimens of the article, or of solutions washings, or extracts thereof to which the test is to be applied do not of themselves inhibit or enhance the reaction or otherwise interfere with the test. Validation is accomplished by testing untreated specimens and specimens to which known and demonstrable amounts of RSE or a CSE have been added, and comparing the results with those obtained with a control consisting of the same RSE or CSE dissolved and serially diluted in LAL reagent water or saline (Water for Injection or Sodium Chloride Injection that does not give a positive response with the LAL reagent used in this test). Appropriate negative controls are included. Use a LAL reagent of confirmed label potency. Confirm the label potency (sensitivity) of the particular LAL reagent with the RSE (or CSE) using not less than 4 replicates, under conditions shown to achieve an acceptable variability of the test, e.g., where the standard deviation of the geometric mean log lysate sensitivity is such that the 99 percent upper limit of the result does not exceed the 99 percent upper limit specified for licensing the LAL reagent (see Proposed Additional Standards, Limulus Amebocyte Lysate, 43 Fed Reg 156, August 11, 1978, applicable to 21 CFR Sec. 660.102 [8] [d]).

Conduct replicated assays of the endotoxin controls and of the specimens to which endotoxin was added as directed under *Procedure*. Record the end-points (E, in Units or Millimits per ml) observed in the replicated assays. Take the logarithms to the end-points of the dilution series used, and compute the geometric means of the log end-points for the control and for specimens containing endotoxin by the formula antilog $\Sigma e/f$, in which Σe is the sum of the log end-points of the dilution series used and f is the number of replicate end-points in each case. The test is valid for the article if the geometric mean value obtained for the specimen

...proximately different from that value for the control, i.e., the ...ding mean end-points are separated by not more than a 5-fold ...ion in the parallel dilution series and have a statistical ...ance determined from the logarithmic values of the observed ...points for the calculation) of 0.05 or less of a true difference ...een the means.

Test Procedure

...e of less than 4 replicates at each level of the dilution series ...the specimen under test. Whether the test is employed as a ...ve or as a quantitative assay, an endotoxin dilution series ...ing not less than 4 replicates is conducted in parallel as a ...ability test. A single set of endotoxin dilution series may serve ...be used for several blocks of limit tests or of assays, provided ...ormal experimental conditions within test blocks are uniform. Where ...ere is a change in the lot of LAL or of standard endotoxins, ...ust be performed satisfactorily lot simultaneously on changeover.

Preparation.—Since the amounts per container of standard endotoxin and of LAL reagent may vary, constitution of contents and ...ubation conditions should be as directed in the labeling. The pH ...the specimen during test is in the range 6.0 to 7.5 unless specifically directed otherwise in the individual monograph. The pH may be adjusted by the addition of sterile, endotoxin-free 0.1 *N* sodium hydroxide or 0.1 *N* hydrochloric acid or suitable buffers.

Procedure.—To 10- × 75-mm test tubes add aliquots of the appropriately constituted LAL reagent, and the specified volumes of solvents, endotoxin standard, positive controls, and negative controls. Swirl gently to mix, and place in an incubating device such as a water bath or heating block, recording the exact time at which the tubes are so placed. Incubate each tube, undisturbed, for 60 ± 2 minutes at 37 ± 1°, and carefully remove it for observation.

Calculation and Interpretation

Gel-clot Readings.—A positive reaction is characterized by the formation of a firm gel that remains firm when inverted through 180°. Record such a result as positive (+). A negative result is characterized by the absence of such a gel or by the formation of a viscous gel that does not maintain its integrity. Record such a result as negative (−). The fine gel structure is susceptible to irreversible breakdown. Handle the tubes with care, and avoid subjecting them to unwanted vibrations, or false negative observations may result in the gel clot test.

Turbidimetric Readings.—Compare absorbances of the test solutions with a standard curve obtained from an endotoxin dilution series when using LAL reagents that have been modified to produce reactions that can be measured turbidimetrically (transmittance at or after using a process for developing a color reaction with the gel or centrifuged precipitate (see *Spectrophotometry and Light-Scattering* ⟨851⟩ and *Color—Instrumental Measurement* ⟨1061⟩), and refer to obtain the concentration of endotoxin present in the solution.

Calculations for Limit Test.—Calculate the concentration of endotoxin in Units or Milliunits per ml or in Units or Milliunits per mg or on the article under test by the formula $(m\lambda)f/\Sigma E$, in which ΣE is the sum of end-point dilution factors expressed as reciprocals, f is the number of replicate end-points, λ is the end-point sensitivity in Units or Milliunits per ml appropriate to the standard endotoxin employed in the assay, and ρ is the corresponding factor for those cases where a specimen of the article cannot be added directly into test but is processed as an extract, solution, or dilution.

Calculations for Assay.—Calculate the concentration of endotoxin in the article under test from the antilog of the mean log end-point values and the confidence limits from the logarithmic values of the observed end-points, or by using any other suitable statistical method (see *Calculation of Potency from a Single Assay*).

Interpretation.—The article meets the requirements of the test for the absence of a firm gel at the level of endotoxin specified in the individual monograph or, where an assay of endotoxin has been made, such result is not more than the maximum ...ount specified in the individual monograph, and the ...nce limits of the assay do not exceed those specified.

⟨91⟩

PANTO

Reference standard.—*Standard*—Dry at 1...

Standard Stock S...—...mg of USP Calcium ...in the dark over pho... protected from abs... 500 ml of water in ...N acetic acid and ...dilute with water ...Calcium Pantoth...

...ator.

Standard Preparation.—On the ... sured volume of *Standard Stock Solution* of ... with sufficient water so that it contains, in each ml, between ... µg and 0.04 µg of calcium pantothenate, the exact concentration being such that the responses obtained as directed under *Procedure* ... 2.0 and 4.0 ml of the *Standard Preparation* being used, are within the linear portion of the log-concentration response curve.

Assay Preparation.—Proceed as directed in the individual monograph for preparing a solution expected to contain approximately the equivalent of the calcium pantothenate concentration in the *Standard Preparation*.

Basal Medium Stock Solution—

Acid-hydrolyzed Casein Solution	25 ml
Cystine-Tryptophane Solution	25 ml
Polysorbate 80 Solution	0.25 ml
Dextrose, Anhydrous	10 g
Sodium Acetate, Anhydrous	5 g
Adenine-Guanine-Uracil Solution	5 ml
Riboflavin–Thiamine Hydrochloride–Biotin Solution	5 ml
Para-aminobenzoic Acid–Niacin–Pyridoxine Hydrochloride Solution	5 ml
Salt Solution A	5 ml
Salt Solution B	5 ml

Dissolve the anhydrous dextrose and sodium acetate in the solutions previously mixed, and adjust with 1 *N* sodium hydroxide to a pH of 6.8. Finally, dilute with water to 250 ml, and mix.

Acid-hydrolyzed Casein Solution.—Mix 100 g of vitamin-free casein with 500 ml of 6 *N* hydrochloric acid, and reflux the mixture for 8 to 12 hours. Remove the hydrochloric acid from the mixture by distillation under reduced pressure until a thick paste remains. Redissolve the resulting paste in water, adjust the solution with 1 *N* sodium hydroxide to a pH of 3.5 ± 0.1, and add water to make 1000 ml. Add 20 g of activated charcoal, stir for 1 hour, and filter. Repeat the treatment with activated charcoal. Store under toluene in a refrigerator at a temperature not below 10°. Filter the solution if a precipitate forms during storage.

Cystine–Tryptophane Solution.—Suspend 4.0 g of L-cystine and 1.0 g of L-tryptophane (or 2.0 g of DL-tryptophane) in 700 to 800 ml of water, heat to 70° to 80°, and add dilute hydrochloric acid (1 in 2) dropwise, with stirring, until the solids are dissolved. Cool and add water to make 1000 ml. Store under toluene in a refrigerator at a temperature not below 10°.

Adenine–Guanine–Uracil Solution.—Dissolve 200 mg each of adenine sulfate, guanine hydrochloride, and uracil, with the aid of heat, in 10 ml of 4 *N* hydrochloric acid, cool, and add water to make 200 ml. Store under toluene in a refrigerator.

Polysorbate 80 Solution.—Dissolve 25 g of polysorbate 80 in alcohol to make 250 ml.

Riboflavin–Thiamine Hydrochloride–Biotin Solution.—Prepare a solution containing, in each ml, 20 µg of riboflavin, 10 µg of thiamine hydrochloride, and 0.04 µg of biotin, by dissolving riboflavin, thiamine hydrochloride, and biotin in 0.02 *N* acetic acid. Store, protected from light, under toluene in a refrigerator.

Para-aminobenzoic Acid–Niacin–Pyridoxine Hydrochloride Solution.—Prepare a solution in neutral 25 percent alcohol to contain 10 µg of para-aminobenzoic acid, 50 µg of niacin, and 40 µg of pyridoxine hydrochloride in each ml. Store in a refrigerator.

Salt Solution A.—Dissolve 25 g of monobasic potassium phosphate and 25 g of dibasic potassium phosphate in water to make 500 ml. Add 5 drops of hydrochloric acid, and store under toluene.

940 Chromatogr... ...stic tubing made of ...solvents and trans... ...be packed with ... solvent vapor ... large chambe... A volume ... for comp... ...ing from the im... ...may be the ... the ...

...s of the standard are uniform and between 20 and 70 mm of ...ercury, and are significantly less than the response to the larger dose of the standard.

Follow the time schedule established during the injection of the standard. Inject alternately a series of five doses consisting of the selected dose of the *Standard Preparation* and an equal-volume dose of the suitably diluted specimen under test. Measure the change in blood pressure following each of the five injections. Calculate the difference between each response to the dose of the test specimen and the mean of the associated doses of the *Standard Preparation* that immediately precede and follow it. The average of the differences is such that the response to the dilution of the test specimen is not greater than that of the dilution of the *Standard Preparation*, and the result corresponds to the limit on pressor activity specified for this test.

⟨141⟩ PROTEIN—BIOLOGICAL ADEQUACY TEST

This test is intended for the evaluation of the biological adequacy, as an index to the completeness of the mixture of amino acids contained, of Protein Hydrolysate Injection.

Depletion Diet—

	Parts by Weight
Dextrin	83.9
Corn Oil	9.0
Salt Mixture	4.0
Agar	2.0
Cod Liver Oil	1.0
Choline Chloride	0.15
Inositol	0.10
Calcium Pantothenate	0.002
Nicotinamide	0.0015
Riboflavin	0.0003
Pyridoxine	0.00025
Thiamine	0.0002
p-Aminobenzoic Acid	0.0002
Folic Acid	0.0002
Menadione	0.0002
Biotin	0.00002

Salt Mixture—Prepare the salt mixture specified in the *Depletion Diet*, as follows:

Sodium Chloride	139.3 g
Potassium Biphosphate	389.0 g
Magnesium Sulfate, Anhydrous	57.3 g
Calcium Carbonate	381.4 g
Ferrous Sulfate	27.0 g
Manganese Sulfate	4.01 g
Potassium Iodide	0.79 g
Zinc Sulfate	0.548 g
Cupric Sulfate	0.477 g
Cobaltous Chloride	0.023 g

Place a portion of the weighed quantity of sodium chloride in a suitable mortar and add, with grinding, the potassium iodide. Set aside the mixture, and mix in a similar manner all the other salts with the remainder of the sodium chloride, adding finally the previously mixed sodium chloride and potassium iodide. Reduce the entire mixture to a fine powder (see *Powder Fineness* ⟨811⟩).

Control Nitrogen Supplement Mixture—Place 50 g of calcium caseinate and 46 g of anhydrous dextrose in a beaker, add sufficient water to make a paste, and finally add 1000 ml of water. Heat the solution between 70° and 82° for 5 minutes with stirring, and cool. Determine nitrogen on an aliquot using *Nitrogen Determination—Method I* or *Method II* ⟨461⟩. Store in a refrigerator. Mix before removing portions for analysis or use.

Depletion and Control Periods—Select a group of not less than 6 male rats 2 to 4 months of age and each weighing between 190 and 225 g. Place the rats in individual cages with free access to the *Depletion Diet* for 12 days. Weigh the depleted rats, and discard any rat that weighs more than 90% of its starting weight.

For the next 3 days substitute as drinking water the *Control Nitrogen Supplement Mixture* in a quantity equivalent to 0.12 g of nitrogen per rat per day, diluted with water to 20 ml, and offered at the same time each morning either in a dish suitable for preventing spillage or in a reservoir fitted with a drinking tube. Remove all drinking water from the cages of the depleted rats during each feeding, and return it after the supplement has been consumed or is removed. On the third day, weigh each rat. Discard any rats that have not consumed all of the *Control Nitrogen Supplement Mixture*.

For the next 3 days, replace the *Control Nitrogen Supplement Mixture* with water ad libitum, and continue the rats on the *Depletion Diet*. Weigh the rats, and discard any that have not lost weight since the previous weighing.

Procedure—Assemble not less than six rats that have completed the depletion and control periods. For 5 days maintain the assembled rats on the *Depletion Diet* with a daily supplement of 20 ml, accurately measured, of a solution containing the Protein Hydrolysate Injection in an amount equivalent to 0.12 g of nitrogen offered each morning in the same way as the *Control Nitrogen Supplement Mixture* was offered previously. Withhold water for at least 2 hours prior to offering the supplement and for 4 hours afterward. Then if the supplement has been consumed, offer water ad libitum.

On the afternoon of the fifth day, weigh each rat, and compare the respective final and starting weights. Not fewer than 80% of the group of rats used gain weight or maintain their weight during the test.

⟨151⟩ PYROGEN TEST

The pyrogen test is designed to limit to an acceptable level the risks of febrile reaction in the patient to the administration, by injection, of the product concerned. The test involves measuring the rise in temperature of rabbits following the intravenous injection of a test solution and is designed for products that can be tolerated by the test rabbit in a dose not to exceed 10 ml per kg injected intravenously within a period of not more than 10 minutes. For products that require preliminary preparation or are subject to special conditions of administration, follow the additional directions given in the individual monograph or, in the case of antibiotics or biologics, the additional directions given in the federal regulations (see *Antibiotics* ⟨1011⟩, and *Biologics* ⟨1041⟩).

Apparatus and Diluents—Render the syringes, needles, and glassware free from pyrogens by heating at 250° for not less than 30 minutes or by any other suitable method. Treat all diluents and solutions for washing and rinsing of devices or parenteral injection assemblies in a manner that will assure that they are sterile and pyrogen-free. Periodically perform control pyrogen tests on representative portions of the diluents and solutions for washing or rinsing of the apparatus.

Temperature Recording—Use an accurate temperature-sensing device such as a clinical thermometer, or thermistor probes or similar probes that have been calibrated to assure an accuracy of ±0.1° and have been tested to determine that a maximum reading is reached in less than 5 minutes. Insert the temperature-sensing probe into the rectum of the test rabbit to a depth of not less than 7.5 cm, and, after a period of time not less than that previously determined as sufficient, record the rabbit's body temperature.

Test Animals—Use healthy, mature rabbits. House the rabbits individually in an area of uniform temperature between 20° and 23° and free from disturbances likely to excite them. The temperature varies not more than ±3° from the selected temperature. Before using a rabbit for the first time in a pyrogen test, condition it not more than seven days before use by a sham test that includes all of the steps as directed under *Procedure* except injection. Do not use a rabbit for pyrogen testing more frequently than once every 48 hours, nor prior to 2 weeks following a maximum rise of its temperature of 0.6° or more while being subjected to the pyrogen test, or following its having been given a test specimen that was adjudged pyrogenic.

Procedure—Perform the test in a separate area designated solely for pyrogen testing and under environmental conditions similar to those under which the animals are housed and free from disturbances likely to excite them. Withhold all food from the rabbits used during the period of the test. Access to water is allowed at all times, but may be restricted during the test. If rectal temperature-measuring probes remain inserted throughout the testing pe-

restrain the rabbits with light-fitting neck stocks that allow rabbits to assume a natural resting posture. Not more than 30 ...s prior to the injection of the test dose, determine the "control ...ature" of each rabbit: this is the base for the determination ...y temperature increase resulting from the injection of a test ...tion. In any one group of test rabbits, use only those rabbits ...e control temperatures do not vary by more than 1° from each ...er, and do not use any rabbit having a temperature exceeding ...°.

Unless otherwise specified in the individual monograph, inject ...o an ear vein of each of three rabbits 10 ml of the test solution per ...g of body weight, completing each injection within 10 minutes after ...art of administration. The test solution is *either* the product, ...constituted if necessary as directed in the labeling, *or* the material ...der test treated as directed in the individual monograph and in...ted in the dose specified therein. For pyrogen testing of devices ...injection assemblies, use washings or rinsings of the surfaces that ...me in contact with the parenterally administered material or with ...e injection site or internal tissues of the patient. Assure that all ...l solutions are protected from contamination. Perform the in...tion after warming the test solution to a temperature of 37 ± 2°. ...Record the temperature at 1, 2, and 3 hours subsequent to the in...tion.

Test Interpretation and Continuation—Consider any temperature ...creases as zero rise. If no rabbit shows an individual rise in ...perature of 0.6° or more above its respective control tempera...e, and if the sum of the three individual maximum temperature ...s does not exceed 1.4°, the product meets the requirements for ...absence of pyrogens. If any rabbit shows an individual tem...erature rise of 0.6° or more, or if the sum of the three individual ...aximum temperature rises exceeds 1.4°, continue the test using ...other rabbits. If not more than three of the eight rabbits show ...dual rises in temperature of 0.6° or more, and if the sum of ...eight individual maximum temperature rises does not exceed ..., the material under examination meets the requirements for ...bsence of pyrogens.

RADIOACTIVE PHARMACEUTICALS

Test Dose for Preformulated, Ready-to-use Products Labeled with Radioactivity

AGGREGATED ALBUMIN AND OTHER PARTICLE-CONTAINING PRODUCTS

...or the rabbit pyrogen test, dilute the product with Sodium ...oride Injection to not less than 100 μCi per ml, and inject a dose ...ml per kg of body weight into each rabbit.

OTHER PRODUCTS

Where Physical Half-life of Radionuclide is Greater Than 1 Day—Calculate the maximum volume of the product that might ...jected into a human subject. This calculation takes into ac...t the maximum recommended radioactive dose of the product, ...Ci, and the radioactive assay, in μCi per ml, of the product at ...piration date or time. Using this information, calculate the ...imum volume dose per kg to a 70-kg human subject.

...or the rabbit pyrogen test, inject a minimum of 10 times this ...e per kg of body weight into each rabbit. If necessary, dilute ...Sodium Chloride Injection. The total injected volume per ...t is not less than 1 ml and not more than 10 ml of solution.

Where Physical Half-life or Radionuclide is Less Than 1 Day—...products labeled with radionuclides having a half-life of less ...1 day, the dosage calculations are identical to those described ...first paragraph under *Other Products*. These products may ...leased for distribution prior to completion of the rabbit pyrogen ...but such test shall be initiated at not more than 36 hours after ...e.

Test Dose for Pharmaceutical Constituents or Reagents to Be Labeled

...following test dose requirements pertain to reagents that are ...Labeled or constituted prior to use by the direct addition of ...ese solutions such as Sodium Pertechnetate Tc 99*m* Injec...cold kits."

...ure that the entire contents of the vial of nonradioactive re...be injected into a 70-kg human subject, or that ½ of the ... total contents per kg will be injected. If the contents are dry, constitute with a measured volume of Sodium Chloride Injection.

For the rabbit pyrogen test, inject ⅓ of the vial contents per kg of body weight into each rabbit. The maximum dose per rabbit is the entire contents of a single vial. The total injected volume per rabbit is not less than 1 ml and not more than 10 ml of solution.

⟨161⟩ TRANSFUSION AND INFUSION ASSEMBLIES

The following tests are provided for application to representative specimens of disposable transfusion and infusion assemblies of tubing.

Sterility—Proceed as directed for *Sterile Devices* under *Sterility Tests* ⟨71⟩.

Pyrogens—Select 10 assemblies representative of the production of each working day, and through the tubing of each pass a separate 40-ml portion of sterile, pyrogen-free saline TS at a flow rate of approximately 10 ml per minute. The pooled effluent meets the requirements of the *Pyrogen Test* ⟨151⟩, the test dose being 10 ml per kg of body weight.

Safety—Select 1 transfusion and infusion assembly representative of the production of each working day. Fill the assembly as completely as practicable with sterile saline TS, clamp the ends securely to retain the solution, and immerse the filled assembly completely in water. Heat the water at not less than 85° for 1 hour. Drain the contents of the assembly, and dilute with sterile saline TS to 250 ml. Inject intravenously 0.5 ml of the solution so prepared into each of five healthy mice weighing between 17 and 23 g: at the end of 4, 24, and 48 hours the animals show no discernible symptoms of toxicity. If any of the animals show gross signs of toxicity or die, repeat the test with another five healthy mice weighing 20 ± 1 g each: all of the animals survive for 48 hours

Other requirements—Those parts of the assemblies that are made of plastic meet the requirements under *Containers* ⟨661⟩.

⟨171⟩ VITAMIN B_{12} ACTIVITY ASSAY

Reference Standard—*USP Cyanocobalamin Reference Standard*—Keep container tightly closed and protected from light. Dry over silica gel for 4 hours before using.

Assay Preparation—Place a suitable quantity of the material to be assayed, previously reduced to a fine powder if necessary and accurately measured or weighed, in an appropriate vessel containing, for each g or ml of material taken, 25 ml of an aqueous extracting solution prepared just prior to use to contain, in each 100 ml, 1.29 g of disodium phosphate, 1.3 g of anhydrous citric acid, and 1.0 g of sodium metabisulfite. Autoclave the mixture at 121° for 10 minutes. Allow any undissolved particles of the extract to settle, and filter or centrifuge, if necessary. Dilute an aliquot of the clear solution with water so that the final test solution contains vitamin B_{12} activity approximately equivalent to that of the *Standard Cyanocobalamin Solution* which is added to the assay tubes.

Standard Cyanocobalamin Stock Solution—To a suitable quantity of USP Cyanocobalamin RS, accurately weighed, add sufficient 25 percent alcohol to make a solution having a known concentration of 1.0 μg of cyanocobalamin per ml. Store in a refrigerator.

Standard Cyanocobalamin Solution—Dilute a suitable volume of *Standard Cyanocobalamin Stock Solution* with water to a measured volume such that after the incubation period as described under *Procedure*, the difference in transmittance between the inoculated blank and the 5.0 ml level of the *Standard Cyanocobalamin Solution* is not less than that which corresponds to a difference of 1.25 mg in dried cell weight. This concentration usually falls between 0.01 ng and 0.04 ng per ml of *Standard Cyanocobalamin Solution*. Prepare a fresh standard solution for each assay.

Basal Medium Stock Solution—Prepare the medium according to the following formula and directions. A dehydrated mixture containing the same ingredients may be used provided that, when constituted as directed in the labeling, it yields a medium compa-

the production of dense, white fumes. Again cool, cautiously add 5 ml of water, mix, and boil gently to the production of dense, white fumes and to a volume of 2 to 3 ml. Cool, dilute cautiously with a few ml of water, add 2.0 ml of *Standard Lead Solution* (20 µg of Pb), and mix. Transfer to a 50-ml color-comparison tube, rinse the flask with water, adding the rinsing to the tube until the volume is 25 ml, and mix.

Test Preparation—

If the substance is a solid—Transfer the quantity of the test substance specified in the individual monograph to a clean, dry, 100-ml Kjeldahl flask [NOTE—A 300-ml flask may be used if the reaction foams excessively], clamp the flask at an angle of 45°, and add sufficient of a mixture of 8 ml of sulfuric acid and 10 ml of nitric acid to moisten the substance thoroughly. Warm gently until the reaction commences, allow the reaction to subside, and add additional portions of the same acid mixture, heating after each addition, until a total of 18 ml of the acid mixture has been added. Increase the amount of heat, and boil gently until the solution darkens. Cool, add 2 ml of nitric acid, and again heat until the solution darkens. Continue the heating, followed by addition of nitric acid until no further darkening occurs, then heat strongly to the production of dense, white fumes. Cool, cautiously add 5 ml of water, boil gently to the production of dense, white fumes, and continue heating until the volume is reduced to a few ml. Cool, cautiously add 5 ml of water, and examine the color of the solution. If the color is yellow, cautiously add 1 ml of 30 percent hydrogen peroxide, and again evaporate to the production of dense, white fumes and a volume of 2 to 3 ml. If the solution is still yellow in color, repeat the addition of 5 ml of water and the peroxide treatment. Cool, dilute cautiously with a few ml of water, and rinse into a 50-ml color-comparison tube, taking care that the combined volume does not exceed 25 ml.

If the substance is a liquid—Transfer the quantity of the test substance specified in the individual monograph to a clean, dry, 100-ml Kjeldahl flask [NOTE—A 300-ml flask may be used if the reaction foams excessively], clamp the flask at an angle of 45°, and cautiously add a few ml of a mixture of 8 ml of sulfuric acid and 10 ml of nitric acid. Warm gently until the reaction commences, allow the reaction to subside, and proceed as directed under *If the substance is a solid*, beginning with "add additional portions of the same acid mixture."

Procedure—Treat the *Test Preparation* and the *Standard Preparation* as follows: Adjust the solution to a pH between 3.0 and 4.0, using short-range pH indicator paper as external indicator, with ammonium hydroxide (a dilute ammonia solution may be used, if desired, as the specified range is approached), dilute with water to 40 ml, and mix.

To each tube add 10 ml of freshly prepared hydrogen sulfide TS, mix, allow to stand for 5 minutes, and view downward over a white surface: the color of the *Test Preparation* is not darker than that of the *Standard Preparation*.

⟨241⟩ IRON

This limit test is provided to demonstrate that the content of iron, in either the ferric or the ferrous form, does not exceed the limit for iron specified in the individual monograph. The determination is made by concomitant visual comparison with a control prepared from a standard iron solution.

Special Reagents—

STANDARD IRON SOLUTION—Dissolve 863.4 mg of ferric ammonium sulfate [$FeNH_4(SO_4)_2 \cdot 12H_2O$] in water, add 10 ml of 2 *N* sulfuric acid, and dilute with water to 100.0 ml. Pipet 10 ml of this solution into a 1000-ml volumetric flask, add 10 ml of 2 *N* sulfuric acid, dilute with water to volume, and mix. This solution contains the equivalent of 0.01 mg (10 µg) of iron per ml.

AMMONIUM THIOCYANATE SOLUTION—Dissolve 30 g of ammonium thiocyanate in water to make 100 ml.

Standard Preparation—Into a 50-ml color-comparison tube pipet 1 ml of *Standard Iron Solution* (10 µg of Fe), dilute with water to 45 ml, add 2 ml of hydrochloric acid, and mix.

Test Preparation—Use the solution prepared as directed in the test for *Iron* in the individual monograph, and transfer it to a 50-ml color-comparison tube.

Procedure—To each of the tubes containing the *Standard Preparation* and the *Test Preparation* add 50 mg of ammonium peroxydisulfate crystals and 3 ml of *Ammonium Thiocyanate Solution*, and mix: the color of the solution from the *Test Preparation* is not darker than that of the solution from the *Standard Preparation*.

⟨251⟩ LEAD

The imposition of stringent limits on the amounts of lead that may be present in pharmaceutical products has resulted in the use of two methods, of which the one set forth following depends upon extraction of lead by solutions of dithizone. For determination of the content of heavy metals generally, expressed as a lead equivalent, see *Heavy Metals* ⟨231⟩.

Select all reagents for this test to have as low a content of lead as practicable, and store all reagent solutions in containers of borosilicate glass. Rinse thoroughly all glassware with warm dilute nitric acid (1 in 2), followed by water.

Special Reagents—

AMMONIA-CYANIDE SOLUTION—Dissolve 2 g of potassium cyanide in 15 ml of stronger ammonia TS, and dilute with water to 100 ml.

AMMONIUM CITRATE SOLUTION—Dissolve 40 g of citric acid in 90 ml of water. Add 2 or 3 drops of phenol red TS, then cautiously add stronger ammonia TS until the solution acquires a reddish color. Remove any lead that may be present by extracting the solution with 20-ml portions of *Dithizone Extraction Solution* (see below), until the dithizone solution retains its orange-green color.

DILUTED STANDARD LEAD SOLUTION—Dilute an accurately measured volume of *Standard Lead Solution* (see ⟨231⟩) [containing 10 µg of lead per ml], with 9 volumes of dilute nitric acid (1 in 100) to obtain a solution that contains 1 µg of lead per ml.

DITHIZONE EXTRACTION SOLUTION—Dissolve 30 mg of dithizone in 1000 ml of chloroform, and add 5 ml of alcohol. Store the solution in a refrigerator.

Before use, shake a suitable volume of the dithizone extraction solution with about half its volume of dilute nitric acid (1 in 100), discarding the nitric acid.

HYDROXYLAMINE HYDROCHLORIDE SOLUTION—Dissolve 20 g of hydroxylamine hydrochloride in sufficient water to make approximately 65 ml. Transfer to a separator, add 5 drops of thymol blue TS, then add ammonium hydroxide until the solution assumes a yellow color. Add 10 ml of sodium diethyldithiocarbamate solution (1 in 25), mix, and allow to stand for 5 minutes. Extract this solution with successive 10- to 15-ml portions of chloroform until a 5-ml portion of the chloroform extract does not assume a yellow color when shaken with cupric sulfate TS. Add 3 *N* hydrochloric acid until the solution is pink (if necessary, add 1 or 2 drops more of thymol blue TS), and then dilute with water to 100 ml.

POTASSIUM CYANIDE SOLUTION—Dissolve 50 g of potassium cyanide in sufficient water to make 100 ml. Remove the lead from this solution by extraction with successive portions of *Dithizone Extraction Solution*, as described under *Ammonium Citrate Solution* above, then extract any dithizone remaining in the cyanide solution by shaking with chloroform. Finally dilute the cyanide solution with sufficient water so that each 100 ml contains 10 g of potassium cyanide.

STANDARD DITHIZONE SOLUTION—Dissolve 10 mg of dithizone in 1000 ml of chloroform. Keep the solution in a glass-stoppered, lead-free bottle, suitably wrapped to protect it from light, and store in a refrigerator.

NOTE—The following special reagents are called for in the test for *Lead* under *Ferrous Sulfate*.

CITRATE-CYANIDE WASH SOLUTION—To 50 ml of water add 50 ml of *Ammonium Citrate Solution* and 4 ml of *Potassium Cyanide Solution*, mix, and adjust the pH, if necessary, with ammonium hydroxide to 9.0.

pH 2.5 BUFFER SOLUTION—To 25.0 ml of 0.2 *M* potassium biphthalate add 37.0 ml of 0.1 *N* hydrochloric acid, and dilute with water to 100.0 ml.

DITHIZONE-CARBON TETRACHLORIDE SOLUTION—Dissolve 10 mg of dithizone in 1 liter of carbon tetrachloride. Prepare this solution on the day of use.

pH 2.5 WASH SOLUTION—To 500 ml of dilute nitric acid (1 in

...pH 2.5 Buffer Solution, and mix.

AMMONIA-CYANIDE WASH SOLUTION—To 35 ml of *pH 2.5 Buffer Solution* add 4 ml of *Ammonia-Cyanide Solution*, and mix.

Test Preparation—Where the monograph does not specify preparation of a solution, prepare a *Test Preparation* as follows: ...Caution—Exercise safety precautions in this procedure, since ... may react with explosive violence when digested with ... peroxide. Transfer 1.0 g of the substance under test to a suitable flask, add 5 ml of sulfuric acid and a few glass beads, and heat on a hot plate in a hood until charring begins. Other suitable means of heating may be substituted. (Add additional sulfuric acid, if necessary, to wet the substance completely, but do not add more than a total of 10 ml.) After the substance has been initially decomposed by the acid, add, dropwise and with caution, 30 percent hydrogen peroxide, allowing the reaction to subside and again cooling between drops. Add the first few drops very slowly, mix carefully to prevent a rapid reaction, and discontinue heating if foaming becomes excessive. Swirl the solution in the flask to prevent uncarbonized substance from caking on the walls of the flask. Add peroxide whenever the mixture turns brown or darkens. Continue the digestion until the substance is completely destroyed, as indicated by dense fumes of sulfur trioxide are evolved, and the solution is colorless. Cool, cautiously add 10 ml of water, evaporate until sulfur trioxide again is evolved, and cool.

Procedure—Transfer the *Test Preparation* or the volume of the weighed sample specified in the monograph to a separator, and, unless otherwise directed in the monograph, add 6 ml of *Ammonium Citrate Solution* and 2 ml of *Hydroxylamine Hydrochloride Solution*. (For the determination of lead in iron salts use 10 ml of *Ammonium Citrate Solution*.) Add 2 drops of phenol red TS, and render the solution just alkaline (red in color) by the addition of ammonium hydroxide. Cool the solution if necessary, and add 2 ml of *Potassium Cyanide Solution*. Immediately extract the solution with 5-ml portions of *Dithizone Extraction Solution*, draining each extract into another separator, until the dithizone solution has a green color. Shake the combined dithizone solutions for 30 seconds with 20 ml of dilute nitric acid (1 in 100), and discard the chloroform layer. Add to the acid solution 5.0 ml of *Standard Lead Solution* and 4 ml of *Ammonia-Cyanide Solution*, and mix. Add 30 seconds: the color of the chloroform layer is of no deeper violet than that of a control made with a volume of *Standard Lead Solution* equivalent to the amount of lead in the sample under examination, and the same quantities of the reagents and in the same manner as in the test with the sample.

⟨261⟩ MERCURY

[Mercuric dithizonate is light-sensitive. Perform this test in subdued light. The addition of acetic acid to the titration helps to stabilize mercuric dithizonate.]

Dithizone Stock Solution—Dissolve 40 mg of dithizone in 1000 ml of chloroform.

Dithizone Titrant—Dilute 30.0 ml of *Dithizone Stock Solution* with chloroform to 100.0 ml. This solution contains approximately 1.2 mg of dithizone per liter.

Mercury Stock Solution—Transfer 135.4 mg of mercuric chloride to a 100-ml volumetric flask, and dilute with 1 *N* sulfuric acid to volume. This solution contains the equivalent of 100 mg of Hg.

Solution for Standardizing Dithizone Titrant—Dilute 10.0 ml of *Mercury Stock Solution* to a 100-ml volumetric flask with 1 *N* sulfuric acid to volume. Each ml of this solution contains the equivalent of 20 µg of Hg.

Standard Lead Solution—Prepare as directed in the solutions called for in the limit test for mercury in the monographs on Ferrous Fumarate, Ferrous Gluconate, Ferrous Sulfate, Ferrous Sulfate Tablets, and Ferrous Sulfate Tablets, Enteric-Coated.

Test for Lead ⟨251⟩.

Diluted Hydrochloric Solution—Prepare as directed in the test for *Lead* ⟨251⟩.

Mercury Solution—On the day of use, quantitatively dilute 10.0 ml of *Mercury Stock Solution* with 1 *N* sulfuric acid to 100.0 ml. Each ml of the resulting solution contains the equivalent of 100 µg of mercury.

Dithizone Extraction Solution—Prepare as directed in the test for *Lead* ⟨251⟩.

Diluted Dithizone Extraction Solution—Just prior to use, dilute 5 ml of *Dithizone Extraction Solution* with 25 ml of chloroform.

Standardization of Dithizone Titrant—Transfer 1.0 ml of *Mercury Solution for Standardizing Dithizone Titrant* to a 250-ml separator, and add 100 ml of 1 *N* sulfuric acid, 90 ml of water, and 10 ml of hydroxylamine hydrochloride solution (1 in 5). Titrate the solution with *Dithizone Titrant* from a 10-ml microburet, shaking the mixture 20 times after each addition and allowing the chloroform layer to separate, then discarding the chloroform layer. Continue until a final addition of *Dithizone Titrant* is green in color after shaking. Calculate the quantity, in µg, of Hg equivalent to each ml of *Dithizone Titrant* by the formula $20/V$, in which V is the volume, in ml, of *Dithizone Titrant* added.

Test Preparation—Transfer about 2 g of the substance under test, accurately weighed, to a glass-stoppered, 250-ml conical flask, add 20 ml of a mixture of equal volumes of nitric acid and sulfuric acid, attach a suitable condenser, reflux the mixture for 1 hour, cool, cautiously dilute with water, and boil until fumes of nitrous acid no longer are noticeable. Cool the solution, cautiously dilute with water, transfer to a 200-ml volumetric flask, dilute with water to volume, mix, and filter.

Procedure—Transfer 50.0 ml of *Test Preparation* to a 250-ml separator, and extract with successive small portions of chloroform until the last chloroform extract remains colorless. Discard the chloroform extract, and add to the extracted *Test Preparation* 50 ml of 1 *N* sulfuric acid, 90 ml of water, and 10 ml of hydroxylamine hydrochloride solution (1 in 5). Proceed as directed under *Standardization of Dithizone Titrant*, beginning with "Titrate the solution." Calculate the amount of mercury.

⟨271⟩ READILY CARBONIZABLE SUBSTANCES TEST

In tests for readily carbonizable substances, unless otherwise directed, add the specified quantity of the substance, finely powdered if in solid form, in small portions to the comparison container, which is made of colorless glass resistant to the action of sulfuric acid and contains the specified volume of sulfuric acid TS (see under *Test Solutions*).

Stir the mixture with a glass rod until solution is complete, allow the solution to stand for 15 minutes, unless otherwise directed, and compare the color of the solution with that of the specified matching fluid in a comparison container which also is of colorless glass and has the same internal and cross-section dimensions, viewing the fluids transversely against a background of white porcelain or white glass.

When heat is directed in order to effect solution of the substance in the sulfuric acid TS, mix the sample and the acid in a test tube, heat as directed, and transfer the solution to the comparison container for matching with the designated Matching Fluid (see ⟨631⟩).

Special attention is directed to the importance of the concentration of sulfuric acid used in this test. The reagent of the required strength, i.e., 95.0 ± 0.5 percent of H_2SO_4, is designated as a "Test Solution."

⟨281⟩ RESIDUE ON IGNITION

Weigh accurately 1 to 2 g of the substance, or the amount specified in the individual monograph, in a suitable crucible that previously has been ignited, cooled, and weighed. Heat, gently at first, until the substance is thoroughly charred, cool, then, unless otherwise directed in the individual monograph, moisten the residue with 1 ml of sulfuric acid, heat gently until white fumes no longer are evolved, and ignite at 600 ± 25° until the carbon is consumed. Cool in a desiccator, weigh, and calculate the percentage of residue. If the amount of the residue so obtained exceeds the limit specified in the individual monograph, again moisten the residue with 1 ml of sulfuric acid, heat and ignite as before, and again calculate the percentage of residue. Continue the ignition until constant weight is attained, unless otherwise specified.

Conduct the ignition in a well-ventilated hood, but protected from

...carefully, and at as low a temperature as is possible to effect the complete combustion of the carbon. A muffle furnace may be used, if desired, and its use is recommended for the final ignition at 800 ± 25°.

⟨291⟩ SELENIUM

Stock Solution—Dissolve 40.0 mg of metallic selenium in 100 ml of dilute nitric acid (1 in 2) in a 1000-ml volumetric flask, warming gently on a steam bath if necessary to effect solution, add water to volume, and mix. Pipet 5 ml of this solution into a 200-ml volumetric flask, add water to volume, and mix. Each ml of the resulting solution contains the equivalent of 1 μg of selenium (Se).

Diaminonaphthalene Solution—Dissolve 100 mg of 2,3-diaminonaphthalene and 500 mg of hydroxylamine hydrochloride in 0.1 *N* hydrochloric acid to make 100 ml. Prepare this solution fresh on the day of use.

Standard Solution—Pipet 6 ml of *Stock Solution* into a 150-ml beaker, and add 50 ml of dilute nitric acid (1 in 60).

Test Solution—Using a 1000-ml combustion flask and using 25 ml of dilute nitric acid (1 in 30) as the absorbing liquid, proceed as directed under *Oxygen Flask Combustion* ⟨471⟩. Upon completion of the combustion, place a few ml of water in the cup, loosen the stopper, and rinse the stopper, the specimen holder, and the sides of the flask with about 10 ml of water. Transfer the solution with the aid of about 20 ml of water to a 150-ml beaker, and heat gently to the boiling temperature. Boil for 10 minutes, and allow the solution to cool to room temperature.

Procedure—Treat the *Standard Solution*, the *Test Solution*, and the reagent blank consisting of 50 ml of dilute nitric acid (1 in 60), concomitantly and in parallel, as follows: Add ammonium hydroxide solution (1 in 2) to adjust to a pH of 2.0 ± 0.2. Dilute with water to 60.0 ml, and transfer to a low-actinic separator with the aid of 10.0 ml of water, adding the 10.0 ml of rinsings to the separator. Immediately add 5.0 ml of *Diaminonaphthalene Solution*, insert the stopper, and swirl to mix. Allow the solution to stand at room temperature for 100 minutes. Add 5.0 ml of cyclohexane, shake vigorously for 2 minutes, and allow the layers to separate. Discard the aqueous layer, and centrifuge the cyclohexane extract to remove any traces of water. Determine the absorbance of each solution in a 1-cm cell at the wavelength of maximum absorbance at about 380 nm, with a suitable spectrophotometer, using cyclohexane as the blank, and compare the absorbances: the absorbance of the *Test Solution* is not greater than that of the *Standard Solution* where a 200-mg test specimen has been taken, or is not greater than one-half that of the *Standard Solution* where a 100-mg test specimen has been taken.

OTHER TESTS AND ASSAYS

⟨301⟩ ACID-NEUTRALIZING CAPACITY

[NOTE—All tests shall be conducted at a temperature of 37 ± 2°, except that tests may be conducted at 25 ± 3° if the results obtained are equivalent.]

Standardization of pH Meter—Standardize a pH meter at pH 4.0 using the appropriate phthalate standardizing buffer as described under *pH* ⟨791⟩, and check for proper operation near pH 7.5.

Magnetic Stirrer—Transfer 100 ml of water to a 250-ml beaker containing a 40-mm × 10-mm magnetic stirring bar that is coated with a solid perfluorocarbon and has a spin ring at its center. Adjust the power setting of the magnetic stirrer to produce a stirring rate of 500 ± 30 rpm when the stirring bar is centered in the beaker, as determined by a suitable optical tachometer.

Test Preparation—

Tablets—Transfer the accurately weighed portion of the subdivided specified in the individual monograph to a 250-ml beaker, add 70 ml of water, and mix on the *Magnetic Stirrer* for 1 minute.

Effervescent Solids—Transfer an accurately weighed quantity, equivalent to the minimum labeled dosage, to a 250-ml beaker, add 10 ml of water, and swirl the beaker gently while allowing the reaction to subside. Add another 10 ml of water, and swirl gently. Wash the walls of the beaker with 50 ml of water, and mix on the *Magnetic Stirrer* for 1 minute.

Suspensions and Other Liquids—Shake the container until the contents are uniform, and determine the density. Transfer an accurately weighed quantity of the uniform mixture, equivalent to the minimum labeled dosage, to a 250-ml beaker, add water to make a total volume of about 70 ml, and mix on the *Magnetic Stirrer* for 1 minute.

Non-chewable Tablets—Weigh not less than 20 tablets, and determine the average tablet weight. Grind the tablets to a powder that passes through a No. 20 sieve and is retained on a No. 100 sieve. Mix the material on the No. 100 sieve to obtain a uniform mixture, transfer an accurately weighed quantity of it, equivalent to the minimum labeled dosage, to a 250-ml beaker. If wetting is desired, add not more than 5 ml of alcohol (neutralized to an apparent pH of 3.5), and mix to wet the specimen thoroughly. Add 70 ml of water, and mix on the *Magnetic Stirrer* for 1 minute.

Chewable Tablets—Prepare as directed for *Non-chewable Tablets*.

Capsules—Weigh accurately not less than 20 capsules. Remove the capsule contents completely, with the aid of a cotton swab if necessary. Accurately weigh the empty capsules, and determine the average weight of the contents per capsule. Mix the combined capsule contents to obtain a uniform mixture, and proceed as directed for *Non-chewable Tablets*, beginning with "transfer an accurately weighed quantity of it."

Procedure—Pipet 30.0 ml of 1.0 *N* hydrochloric acid VS into the *Test Preparation* while continuing to stir with the *Magnetic Stirrer*. Stir for 15 minutes, accurately timed, after the addition of the acid, begin to titrate immediately, and in a period not to exceed an additional 5 minutes, titrate the excess hydrochloric acid with 0.5 *N* sodium hydroxide VS to attain a stable (for not less than 15 seconds) pH of 3.5. Calculate the number of mEq of acid consumed, and express the result in terms of mEq of acid consumed per g of the substance tested. Each ml of 1.0 *N* hydrochloric acid is equal to 1 mEq of acid consumed.

⟨311⟩ ALGINATES ASSAY

Apparatus—The apparatus required is shown in the accompanying diagram. It consists essentially of a soda lime column, *A*, a mercury valve, *B*, connected through a side arm to a reaction flask, *D*, by means of a rubber connection, *C*. Flask *D* is a 100-ml round-bottom, long-neck boiling flask, resting in a suitable heating mantle, *E*.

The reaction flask is provided with a reflux condenser, *F*, to which is fitted a delivery tube, *G*, of 40-ml capacity, having a stopcock, *H*. The reflux condenser terminates in a trap, *I*, containing 25 g of 20-mesh zinc or tin, which can be connected with an absorption tower, *J*.

The absorption tower consists of a 45-cm tube fitted with a medium-porosity, sintered-glass disk sealed to the inner part above the side arm and having a delivery tube sealed to it extending down to the end of the tube. A trap, consisting of a bulb of approximately 100-ml capacity, is blown above the sintered-glass disk, and the outer portion of a ground spherical joint is sealed on above the bulb. A 250-ml conical flask, *K*, is connected to the bottom of the absorption tower. The top of the tower is connected to a soda lime tower, *L*, which is connected to a suitable pump to provide vacuum and air supply, the selection of which is made by a three-way stopcock, *M*. The volume of air or vacuum is controlled by a capillary-tube regulator or needle valve, *N*.

All joints are size $^{35}/_{25}$, ground spherical type.

Procedure—Unless otherwise directed, transfer a specimen of about 250 mg, previously dried in vacuum for 4 hours at 60° and accurately weighed, into the reaction flask, *D*, add 25 ml of dilute hydrochloric acid (1 in 120), insert several boiling chips, and connect the flask to the reflux condenser, *F*, using phosphoric acid as a lubricant. [NOTE—Stopcock grease may be used for the other connections.] Check the system for air leaks by forcing mercury up into the inner tube of the mercury valve, *B*, to a height of about

1. Limits for Glass Types I, II, and III and Plastic Classes I–VI

Nominal Size (in ml)	Maximum Permissible Loss in Transmission at Any Wavelength between 290 nm and 450 nm	
	Flame-sealed Containers	Closure-sealed Containers
1		
2	50	25
5	45	20
10	40	15
20	35	13
50	30	12
15		10

Any container of a size intermediate to those listed above a transmission not greater than that of the next larger size listed in the table. For containers larger than 50 ml, the 50 ml apply.

normal to the surface of the section and reflection losses are minimum.

sure the transmittance of the section with reference to air spectral region of interest, continuously with a recording in- or at intervals of about 20 nm with a manual instrument, region of 290 nm to 450 nm.

The observed light transmission does not exceed the given in Table 1 for containers intended for parenteral use. observed light transmission for containers of Type NP glass or plastic containers for products intended for oral or topical ration does not exceed 10% at any wavelength in the range 290 nm to 450 nm.

CHEMICAL RESISTANCE—GLASS CONTAINERS

following tests are designed to determine the resistance to ace of new (not previously used) glass containers. The of attack is determined by the amount of alkali released from under the influence of the attacking medium under the ons specified. This quantity of alkali is extremely small in ase of the more resistant glasses, thus calling for particular to all details of the tests and the use of apparatus of high and precision. The tests should be conducted in an area ly free from fumes and excessive dust.

Types—Glass containers suitable for packaging Pharmaparations may be classified as in Table 2 on the basis of set forth in this section. Containers of Type I borosilicate are generally used for preparations that are intended for parenteral administration. Containers of Type I glass, or of Type II glass, i.e., soda-lime glass that is suitably de-alkalized, are usually used for packaging acidic and neutral parenteral preparations. Type I glass containers, or Type II glass containers (where stability data demonstrate their suitability), are used for alkaline parenteral preparations. Type III soda-lime glass containers usually are not used for parenteral preparations, except where suitable stability test data indicate that Type III glass is satisfactory for the parenteral preparations that are packaged therein. Containers of Type NP glass are intended for packaging nonparenteral articles; i.e., those intended for oral or topical use.

2. Glass Types and Test Limits

	General Description[a]	Type of Test	Limits	
			Size,[b] ml	ml of 0.020 *N* Acid
I	Highly resistant, borosilicate glass	*Powdered Glass*	All	1.0
II	Treated soda-lime glass	*Water Attack*	100 or less	0.7
			Over 100	0.2
III	Soda-lime glass	*Powdered Glass*	All	8.5
NP	General-purpose soda-lime glass	*Powdered Glass*	All	15.0

[a] Description applies to containers of this type of glass usually

[b] Applies to containers of this type of glass usually

Apparatus—

AUTOCLAVE—For these tests, use an autoclave capable of maintaining a temperature of 121 ± 0.5°, equipped with a thermometer, a pressure gauge, a vent cock, and a rack adequate to accommodate at least 12 test containers above the water level.

MORTAR AND PESTLE—Use a hardened-steel mortar and pestle, made according to the specifications in the accompanying illustration.

OTHER EQUIPMENT—Also required are 20.3-cm (8-inch) sieves made of stainless steel including the No. 20, No. 40, and No. 50 sieves along with the pan and cover (see *Openings of Standard Sieves* ⟨811⟩), 250-ml conical flasks made of resistant glass aged as specified, a 900-g (2-lb) hammer, a permanent magnet, a desiccator, and adequate volumetric apparatus.

Reagents—

HIGH-PURITY WATER—The water used in these tests has a conductivity at 25°, as measured in an in-line cell just prior to dispensing, of not greater than 0.15 μmho per cm. It meets the requirements of the test for *Heavy metals* under *Purified Water*, and is free from copper. The water may be prepared by passing distilled water through a de-ionizer cartridge packed with a mixed bed of nuclear-grade resin, then through a cellulose ester membrane having openings not exceeding 0.45 μm.[2] Do not use copper tubing. Flush the discharge lines before water is dispensed into test vessels. When the low conductivity specification can no longer be met, replace the de-ionizer cartridge.

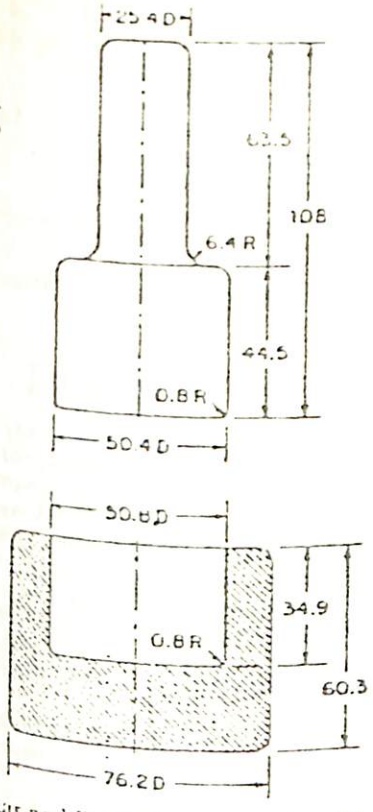
METHYL RED SOLUTION—Dissolve 24 mg of methyl red sodium in purified water to make 100 ml. If necessary, neutralize the solution with 0.02 *N* sodium hydroxide so that the titration of 100 ml of *High-purity Water*, containing 5 drops of indicator, does not require more than 0.020 ml of 0.020 *N* sodium hydroxide to effect the color change of the indicator, which should occur at a pH of 5.6.

Powdered Glass Test

Rinse thoroughly with Purified Water 6 or more containers selected at random, and dry them with a stream of clean, dry air. Crush the containers into fragments about 25 mm in size, divide about 100 g of the coarsely crushed glass into three approximately equal portions, and place one of the portions in the special mortar. With the pestle in place, crush the glass further by striking 3 or 4 blows with the hammer. Nest the sieves, and empty the mortar into the No. 20 sieve. Repeat the operation on each of the two remaining portions of glass, emptying the mortar each time into the No. 20 sieve. Shake the sieves for a short time, then remove the glass from the No. 20 and No. 40 sieves, and again crush and sieve as before. Repeat again this crushing and sieving operation. Empty the receiving pan, reassemble the nest of sieves, and shake on a mechanical sieve shaker for 5 minutes or by hand for an equivalent length of time. Transfer the portion retained on the No. 50 sieve, which should weigh in excess of 10 g, to a closed container, and store in a desiccator until used for the test.

[2] A suitable nuclear-grade resin mixture of the strong acid cation exchanger in the hydrogen form and the strong base anion exchanger in the hydroxide form, with a one-to-one cation to anion equivalence ratio, is available from the Millipore Corp., Bedford, Mass. 01730; Barnstead Co., 225 Rivermoor St., Boston, Mass. 02132; Illinois Water Treatment Co., 840 Cedar St., Rockford, Ill. 61105; and Vaponics, Inc., 200 Cordage Park, Plymouth, Mass. 02360.

A suitable in-line filter is available from the Millipore Corp.; Gelman Instrument Co., 600 S. Wagner Rd., Ann Arbor, Mich. 48106; and Schleicher and Schuell, Inc., 540 Washington St.,



Special Mortar and Pestle for Pulverizing Glass*

* A suitable mortar and pestle is available (catalog No. H-17280) from Humboldt Manufacturing Co., 7300 West Agatite, Norridge, Chicago, Ill. 60656.

...reak the specimen on a piece of glazed paper, and pass a ...net through it to remove particles of iron that may be introduced ...ring the crushing. Transfer the specimen to a 250-ml conical ...k of resistant glass, and wash it with six 30-ml portions of ace...ing each time for about 30 seconds and carefully de...ing the acetone. After washing, the specimen should be free ...n agglomerations of glass powder, and the surface of the grains ...ld be practically free from adhering fine particles. Dry the ...n and contents for 20 minutes at 140°, transfer the grains to a ...ering bottle, and cool in a desiccator. Use the test specimen ...n 48 hours after drying.

Procedure—Transfer 10.00 g of the prepared specimen, accu...ely weighed, to a 250-ml conical flask that has been digested ...d 24 hours previously with *High-purity Water* in a bath at 90° for at ...st 24 hours or at 121° for 1 hour. Add 50.0 ml of *High-purity* ...er to this flask and to one similarly prepared to provide a blank. ...ll flasks with borosilicate glass beakers that previously have ...n tested as described for the flasks and that are of such size that ...y bottoms of the beakers fit snugly down on the top rims of the ...sks. Place the containers in the autoclave, and close it se...ly, leaving the vent cock open. Heat until steam issues vigor...from the vent cock, and continue heating for 10 minutes. ...n the vent cock, and adjust the temperature to 121°, taking 19 ...utes to reach the desired temperature. Hold the tem...ture at 121 ± 2.0° for 30 minutes, counting from the time this ...perature is reached. Reduce the heat so that the autoclave cools ...omes to atmospheric pressure in 38 to 46 minutes, being vented ...ecessary to prevent the formation of a vacuum. Cool the flask ...ntaining water, decant the water from the flask into a ...ll cleansed vessel, and wash the residual powdered glass with ...ll portions of *High-purity Water*, adding the decanted ...ings to the main portion. Add 5 drops of *Methyl Red Solu...* and titrate immediately with 0.020 *N* sulfuric acid. If the ...ume of titrating solution is expected to be less than 10 ml, use a ...ret. Record the volume of 0.020 *N* sulfuric acid used to ...ize the extract from 10 g of the prepared specimen of glass, ...ected for a blank. The volume does not exceed that indicated ...ble 2 for the type of glass concerned.

Water Attack at 121°

...roughly 3 or more containers, selected at random, twice ...Purified Water

Procedure—Fill each container to 90% of its overflow capacity with *High-purity Water*, and proceed as directed for *Procedure* under *Powdered Glass Test*, beginning with "Cap all flasks," except that the time of autoclaving shall be 60 minutes instead of 30 minutes, and ending with "to prevent the formation of a vacuum." Empty the contents from 1 or more containers into a 100-ml graduated cylinder, combining, in the case of smaller containers, the contents of several containers to obtain a volume of 100 ml. Place the pooled specimen in a 250-ml conical flask of resistant glass, add 5 drops of *Methyl Red Solution*, and titrate, while warm, with 0.020 *N* sulfuric acid. Complete the titration within 60 minutes after opening the autoclave. Record the volume of 0.020 *N* sulfuric acid used, corrected for a blank obtained by titrating 100 ml of *High-purity Water* at the same temperature and with the same amount of indicator. The volume does not exceed that indicated in Table 2 for the type of glass concerned.

BIOLOGICAL TESTS—PLASTICS

The following biological test procedures are designed to test the suitability of plastic materials intended for use in fabricating containers or accessories thereto, for parenteral preparations, and to test the suitability of polymers for medical use in implants, devices, and other systems. The procedures provided test the reaction of living animal tissue and of normal animals to the presence of portions of the plastic or extracts of it.

For the purpose of this chapter, these definitions apply: The *Sample* is the plastic specimen under test or an extract prepared from such a specimen. A *Blank* consists of the same quantity of the same extracting medium that is used for the extraction of the specimen under test, treated in the same manner as the extracting medium containing the specimen under test. A *Negative Control*[3] is a plastic specimen that gives no reaction under the conditions of the test.

On the basis of response to the biological test procedures (see *Systemic Injection Test*, *Intracutaneous Test*, *Implantation Test*), six general classes of plastics are defined in Table 3. This classification does not apply to plastics that are intended for use as containers for oral or topical products, or that may be used as an integral part of a drug formulation.

Factors such as plastic composition, processing and cleaning procedures, contacting media, inks, adhesives, absorption, adsorption and permeability of preservatives, and conditions of storage may also affect the suitability of a plastic for a specific use. Evaluation of such factors should be made by appropriate additional specific tests to determine the suitability of a plastic for its intended use.

With the exception of the *Implantation Test*, the procedures are based on the use of extracts which, depending on the heat resistance of the plastic, are prepared at one of three standard temperatures: 50°, 70°, and 121°. Therefore, the class designation of a plastic must be accompanied by an indication of the temperature of extraction; e.g., IV–121°, which represents a class IV plastic extracted at 121°, or I–50°, which represents a class I plastic extracted at 50°.

The *Systemic Injection Test* and the *Intracutaneous Test* are designed to determine the biological response of animals to plastics by the single-dose injection of specific extracts prepared from a *Sample*. The *Implantation Test* is designed to evaluate the reaction of living tissue to the plastic by the implantation of the *Sample* itself into animal tissue. It is essential not only to use the designated amount of the plastic, but also to make available the specified surface for extraction at the stated temperature. Also, it is essential to exercise care in the preparation of the materials to be injected, to prevent contamination with microorganisms and other foreign matter. The proper preparation and placement of the specimens under aseptic conditions are important in the conduct of the *Implantation Test*.

These tests are designed for application to plastics in the condition in which they are used. If a plastic is to be exposed to any cleansing or sterilization process prior to its end-use, then the tests are to be conducted on a *Sample* prepared from a specimen pre-conditioned by the same processing.

Extracting Media —

SODIUM CHLORIDE INJECTION (see monograph).

1 in 20 SOLUTION OF ALCOHOL IN *Sodium Chloride Injection*.

[3] USP Negative Control Plastic RS

Acceptance Table

Stage	Number Tested	Acceptance Criteria
S_1	6	Each unit is not less than $Q + 5\%$.
S_2	6	Average of 12 units ($S_1 + S_2$) is equal to or greater than Q, and no unit is less than $Q - 15\%$
S_3	12	Average of 24 units ($S_1 + S_2 + S_3$) is equal to or greater than Q, and not more than 2 units are less than $Q - 15\%$.

centages of the labeled content so that these values and Q are in the same terms.

⟨721⟩ DISTILLING RANGE

To determine the range of temperatures within which an official liquid distils, or the percentage of the material that distils between two specified temperatures, use Method I or Method II as directed herein. The *lower limit* of the range is the temperature indicated by the thermometer when the first drop of condensate leaves the tip of the condenser, and the *upper limit* is the Dry Point, i.e., the temperature at which the last drop of liquid evaporates from the lowest point in the distillation flask, without regard to any liquid remaining on the side of the flask, or the temperature observed when the proportion specified in the individual monograph has been collected.

[NOTE—Cool all liquids that distil below 80° to between 10° and 15° before measuring the sample to be distilled.]

Method I

Apparatus—Use apparatus similar to that specified for *Method II*, except that the distilling flask is of 50- to 60-ml capacity, and the neck of the flask is 10 to 12 cm long and 14 to 16 mm in internal diameter. The perforation in the upper asbestos board, if one is used, should be such that when the flask is set into it, the portion of the flask below the upper surface of the asbestos has a capacity of 3 to 4 ml.

Procedure—Proceed as directed for *Method II*, but place in the flask only 25 ml of the liquid to be tested.

Method II

Apparatus—Use an apparatus consisting of the following parts:

Distilling Flask—A round-bottom distilling flask, of heat-resistant glass, of 200-ml capacity, and having a total length of 17 to 19 cm and an inside neck diameter of 20 to 22 mm. Attached about midway on the neck, approximately 12 cm from the bottom of the flask, is a side-arm 10 to 12 cm long and 5 mm in internal diameter, which forms an angle of 70° to 75° with the lower portion of the neck.

Condenser—A straight glass condenser 55 to 60 cm in length with a water jacket about 40 cm in length, or a condenser of other design having equivalent condensing capacity. The lower end of the condenser may be bent to provide a delivery tube, or it may be connected to a bent adapter that serves as a delivery tube.

Asbestos Boards—Two pieces of asbestos board, 5 to 7 mm thick and 14 to 16 cm square, suitable for confining the heat to the lower part of the flask. Each board has a hole in its center, and the two boards differ only with respect to the diameter of the hole, i.e., the diameters are 4 and 10 cm, respectively. In use, the boards are placed one upon the other, and resting on a tripod or other suitable support, with the board having the larger hole on top.

Receiver—A 100-ml cylinder graduated in 1-ml subdivisions.

Thermometer—In order to avoid the necessity for an emergent stem correction, an accurately standardized, partial-immersion thermometer having the smallest practical subdivisions (not greater than 0.2°) is recommended. Suitable thermometers are available as the ASTM E-1 series 37C through 41C, and 102C through 107C (see *Thermometers* ⟨21⟩). When placed in position, the stem is located in the center of the neck and the top of the bulb is just below the bottom of the outlet to the side-arm.

Heat Source—A small Bunsen burner or an electric heater or mantle capable of adjustment comparable to that possible with a Bunsen burner.

Procedure—Assemble the apparatus, and place in the flask 100 ml of the liquid to be tested, taking care not to allow any of the liquid to enter the side-arm. Insert the thermometer, shield the entire burner and flask assembly from external air currents, and apply heat, regulating it so that between 5 and 10 minutes elapse before the first drop of distillate falls from the condenser. Continue the distillation at a rate of 4 to 5 ml of distillate per minute, collecting the distillate in the receiver. Note the temperature when the first drop of distillate falls from the condenser, and again when the last drop of liquid evaporates from the bottom of the flask or when the specified percentage has distilled over. Correct the observed temperature readings for any variation in the barometric pressure from the normal (760 mm), adding if the pressure is lower or subtracting if the pressure is higher than 760 mm, and apply the emergent stem correction where necessary. Unless otherwise specified in the individual monograph, allow 0.1° for each 2.7 mm of variation.

⟨731⟩ LOSS ON DRYING

The procedure set forth in this chapter determines the amount of volatile matter of any kind that is driven off under the conditions specified. For substances appearing to contain water as the only volatile constituent, the procedure given in the chapter, *Water Determination* ⟨921⟩, is appropriate, and is specified in the individual monograph.

Unless otherwise directed in the monograph, conduct the determination on 1 to 2 g of the substance, previously mixed and accurately weighed. If the test specimen is in the form of large crystals, reduce the particle size to about 2 mm by quickly crushing. Tare a glass-stoppered, shallow weighing bottle that has been dried for 30 minutes under the same conditions to be employed in the determination. Put the test specimen in the bottle, replace the cover, and accurately weigh the bottle and the contents. By gentle, sidewise shaking distribute the test specimen as evenly as practicable to a depth of about 5 mm generally, and not over 10 mm in the case of bulky materials. Place the loaded bottle in the drying chamber, removing the stopper and leaving it also in the chamber. Dry the test specimen at the temperature and for the time specified in the monograph. [NOTE—The temperature specified in the monograph is to be regarded as being within the range of ±2° of the stated figure.] Upon opening the chamber, close the bottle promptly and allow it to come to room temperature in a desiccator before weighing.

If the substance melts at a lower temperature than that specified for the determination of *Loss on drying*, maintain the bottle with its contents for 1 to 2 hours at a temperature 5° to 10° below the melting temperature, then dry at the specified temperature.

Where the individual monograph directs that loss on drying be determined by thermogravimetric analysis, a sensitive electrobalance is to be used.

Where drying in vacuum over a desiccant is directed in the individual monograph, a vacuum desiccator or a vacuum drying pistol, or other suitable vacuum drying apparatus, is to be used.

Where drying in a desiccator is specified, exercise particular care to ensure that the desiccant is kept fully effective by frequent replacement.

⟨733⟩ LOSS ON IGNITION

This procedure is provided for the purpose of determining the percentage of test material that is volatilized and driven off under the conditions specified. The procedure, as generally applied, is nondestructive to the substance under test; however, the substance may be converted to another form such as an anhydride.

Perform the test on finely powdered material, and break up lumps, if necessary, with the aid of a mortar and pestle before weighing the specimen. Weigh the specimen to be tested without further treatment, unless a preliminary drying at a lower temperature, or other special pretreatment, is specified in the individual monograph. Unless other equipment is designated in the individual monograph, conduct the ignition in a suitable muffle furnace or oven that is capable of maintaining a temperature within 25° of that required for the test, and use a suitable crucible, complete with

⟨781⟩ OPTICAL ROTATION

...ally drug... in a pure state or in a solution, are optically active ...sense that they cause incident plane polarized light to emerge ...ent in planes at different intensities such that the plane ...maximum intensity forms a measurable angle with the plane of ...ident light. Where this effect is large enough for precise ...surement, it may serve as the basis for an assay or an identity ...The optical rotation is expressed in degrees, as either *angular ...on* (observed) or *specific rotation* (calculated with reference ...the specific concentration of 1 g of solute in 1 ml of solution, ...ed under stated conditions). Substances that cause the light ...to rotate clockwise, as viewed toward the light source, are ...dextrorotatory and the *angular rotation* is designated (+). ...hat cause counter-clockwise rotation are termed levorotatory ...ding *angular rotation* is designated (−).

...ion for rotation usually is expressed by the term $[\alpha]_\lambda^t$, in which ...type units, in degrees centigrade (Celsius), the temperature at ...which rotation is determined, and λ represents the characteristic ...spectral line or wavelength of the light used. Unless otherwise ...specified, the values cited in this Pharmacopeia relate to measure... ...made at 25° with the use of the D line of sodium (a doublet at 589.0 ...and 589.6 nm).

The accuracy and precision of optical rotatory measurements will be increased if they are carried out with due regard for the following ...general considerations.

The instrument itself must be in good condition. Optical ele... ...ments must be brilliantly clean and in exact alignment. The match ...point should be close to the normal zero mark. The light source ...should be rigidly set and well aligned with respect to the optical ...path. It should be supplemented by a filtering system capable of ...illuminating light of a sufficiently monochromatic nature. Preci... ...polarimeters generally are designed to accommodate inter... ...changeable disks to isolate the D line from sodium light or the ...546.1-nm line from the mercury spectrum. With polarimeters not ...so designed, cells containing suitably colored liquids may be ...employed as filters. Temperature control of the solution and of the ...polarimeter requires special attention, since rotatory power varies ...appreciably with temperature. The temperature specified for the ...determination applies to the solution, and is maintained within 0.2° ...of the stated value. Accuracy is assured by calibration of the in... ...strument with suitable standards.* Generally a polarimeter ca... ...pable of giving replicate readings within 0.020° suffices for Phar... ...maceutical purposes.

Polarimeter tubes should be filled in such a way as to avoid ...trapping or leaving air bubbles that interfere with the passage of the ...beam of light. Interference from bubbles is minimized with tubes ...in which the bore is expanded at one end. However, with tubes of ...uniform bore, such as semimicro or micro tubes, care is required ...to secure proper filling. Non-metallic tubes are recommended for use ...in making corrosive articles or solutions of articles in corrosive sol...vents.

In closing tubes having removable end-plates fitted with gaskets ...and caps, the latter should be tightened only enough to ensure a ...liquid-proof seal between the end-plate and the body of the tube. ...Excessive pressure on the end-plate may set up strains that result ...in interference with the measurement. In determining the specific ...rotation of a substance of low rotatory power, it is desirable to loosen ...the caps and tighten them again between successive readings in the ...measurement of both the rotation and the zero point. Differences ...resulting from end-plate strain thus generally will be revealed, and ...appropriate adjustments to eliminate the cause may be made.

Procedure— Where the substance is a liquid, adjust its temper... ...ature to 25°, and transfer it to the polarimeter tube. Proceed as ...directed below, beginning with "Make at least five readings," but ...omit the blank determination on the empty, dry tube.

Where the substance is a solid, accurately weigh a suitable portion ...and transfer it to a volumetric flask by means of water, or other ...solvent if specified, reserving a portion of the solvent for the blank ...determination. Add enough solvent to bring the meniscus close to ...but still below the mark, and adjust the flask contents to 25° as by ...immersing the flask in a constant-temperature bath. Add solvent ...to the mark, and mix. Transfer the solution to the polarimeter tube ...within 30 minutes from the time the substance was dissolved, taking ...care to standardize the elapsed time in the case of substances known ...to undergo racemization or mutarotation. During the elapsed time ...interval, maintain the solution at a temperature of 25°.

Make at least five readings, at 25°, of the observed rotation. Substitute the selected solvent for the solution, and make an equal number of readings on it. The zero correction is the average of the blank readings, and is subtracted from the average observed rotation. It is necessary in this calculation to use the observed signs of rotation, whether positive or negative, to give the corrected observed rotation.

Where an automatic photoelectric polarimeter that possesses the necessary degree of accuracy and precision is employed, the need for five or more repetitive readings is obviated.

Calculation— Calculate the specific rotation of a liquid substance, or of a solid in solution, by application of one of the following formulas:

I. For liquid substances, $[\alpha]_\lambda^t = \frac{a}{ld}$;

II. For solutions, $[\alpha]_\lambda^t = \frac{100a}{lpd} = \frac{100a}{lc}$;

in which a is the corrected observed rotation, in degrees, at temperature t at wavelength λ; l is the length of the polarimeter tube, in decimeters; d is the specific gravity of the liquid or solution at the temperature of observation; p is the concentration of the solution expressed as the number of g of substance in 100 g of solution, and c is the concentration of the solution expressed as the number of g of substance in 100 ml of solution.

⟨785⟩ OSMOLARITY

Osmotic pressure is fundamentally related to all biological processes that involve diffusion of solutes or transfer of fluids through membranes. Thus, knowledge of the osmolar concentrations of parenteral fluids is essential. The labels of Pharmacopeial solutions that provide intravenous replenishment of fluid, nutrient(s), or electrolyte(s), as well as of the osmotic diuretic Mannitol Injection, are required to state the osmolar concentration.

The declaration of osmolar concentration on the label of a parenteral solution serves primarily to inform the practitioner whether the solution is hypo-osmotic, iso-osmotic, or hyper-osmotic. A quantitative statement facilitates calculation of the dilution required to render a hyper-osmotic solution iso-osmotic. It also simplifies many calculations involved in peritoneal dialysis and hemodialysis procedures. The osmolar concentration of an extemporaneously compounded intravenous solution prepared in the pharmacy (e.g., a hyperalimentation solution) from osmolar-labeled solutions also can be obtained simply by summing the osmols contributed by each constituent.

The units of osmolar concentration are usually expressed as milliosmols (abbreviation: mOsm) of solute per liter of solution. In general terms, the weight of a substance divided by the number of ions or chemical species (n) formed upon dissolution. In ideal solutions, for example, $n = 1$ for glucose, $n = 2$ for sodium chloride or magnesium sulfate, $n = 3$ for calcium chloride, and $n = 4$ for sodium citrate.

The ideal osmolar concentration may be determined according to the formula:

$$\text{osmolar concentration (mOsm/liter)} = \frac{\text{wt. of substance (g/liter)}}{\text{mol. wt. (g)}} \times \text{number of species} \times 1000$$

As the concentration of the solute increases, interaction among solute particles increases, and actual osmolar values decrease when compared to ideal values. Deviation from ideal conditions is usually slight in solutions within the physiologic range and for more dilute solutions, but for highly concentrated solutions the actual osmolarities may be appreciably lower than ideal values. For example, the ideal osmolarity of 0.9% Sodium Chloride Injection is 9/58.4 × 2 × 1000 = 308 mOsm per liter. In fact, however, n is slightly less than 2 for solutions of sodium chloride, and the actual measured osmolarity of 0.9% Sodium Chloride Injection is about 280 mOsm per liter.

The theoretical osmolarity of a complex mixture, such as Protein Hydrolysate Injection, cannot be readily calculated. In such in

* Suitable calibrations are available from the Office of Standard Reference Materials, National Bureau of Standards, Washington, D.C. 20234. Standard Reference Material 41b, Dextrose, and Standard Reference Material 17a, Sucrose.

[illegible] actual values of osmolar [illegible] to be used to meet the labeling requirement set forth in the individual monographs. They are determined by calculating the osmolarity from measured values of osmolal concentration and water content. Each osmol of solute added to 1 kg of water lowers the freezing point approximately 1.86° and lowers the vapor pressure approximately 0.3 mm of mercury (at 25°). These physical changes are measurable, and they permit accurate estimations of osmolal concentrations.

Where osmometers that measure the freezing-point depression are employed, a measured volume of solution (usually 2 ml) is placed in a glass tube immersed in a temperature-controlled bath. A thermistor and a vibrator are lowered into the mixture, and the temperature of the bath is decreased until the mixture is supercooled. The vibrator is activated to induce crystallization of the water in the test solution, and the released heat of fusion raises the temperature of the mixture to its freezing point. By means of a Wheatstone bridge, the recorded freezing point is converted to a measurement in terms of millіosmolality, or its near equivalent for dilute solutions, milliosmolarity. The instrument is calibrated by using two standard solutions of sodium chloride that span the expected range of osmolarities.

Osmometers that measure the vapor pressures of solutions are less frequently employed. They require a smaller volume of specimen (generally about 5 μl), but the accuracy and precision of the resulting osmolality determination are comparable to those obtained by the use of osmometers that depend upon the observed freezing points of solutions.

Labeling—Where an osmolarity declaration is required in the individual monograph, the label states the total osmolar concentration in milliosmols per liter. Where the contents are less than 100 ml, or where the label states that the article is not for direct injection but is to be diluted before use, the label alternatively may state the total osmolar concentration in milliosmols per ml.

⟨791⟩ pH

For compendial purposes, pH is defined as the value given by a suitable, properly standardized, potentiometric instrument (pH meter) capable of reproducing pH values to 0.02 pH unit using an indicator electrode sensitive to hydrogen-ion activity, the glass electrode, and a suitable reference electrode such as calomel or silver-silver chloride. The instrument should be capable of sensing the potential across the electrode pair and, for pH standardization purposes, applying an adjustable potential to the circuit by manipulation of "standardization," "zero," "asymmetry," or "calibration" control, and should be able to control the change in millivolts per unit change in pH reading through a "temperature" and/or "slope" control. Measurements are made at 25 ± 2°, unless otherwise specified in the individual monograph or herein.

The pH scale is defined by the equation $pH = pHs + (E - Es)/k$, in which E and Es are the measured potentials where the galvanic cell contains the solution under test, represented by pH, and the appropriate *Buffer Solution for Standardization*, represented by pHs, respectively. The value of k is the change in potential per unit change in pH and is theoretically $[0.05916 + 0.000198(t - 25°)]$ volts at any temperature t. This operational pH scale is established by assigning rounded pH values to the *Buffer Solutions for Standardization* from the corresponding National Bureau of Standards molal solutions.

It should be emphasized that the definitions of pH, the pH scale, and the values assigned to the *Buffer Solutions for Standardization* are for the purpose of establishing a practical, operational system so that results may be compared between laboratories. The pH values thus measured do not correspond exactly to those obtained by the classical definition, $pH = -\log [H^+(aq)]$. So long as the solution being measured is sufficiently similar in composition to the buffer used for standardization, the operational pH corresponds fairly closely to the theoretical pH. Although no claim is made with respect to the suitability of the system for measuring hydrogen-ion activity or concentration, the values obtained are closely related to the activity of the hydrogen ion in aqueous solutions.

Where a pH meter is standardized by use of an aqueous buffer and then used to measure the "pH" of a nonaqueous solution or suspension, the ionization constant of the acid or base, the dielectric constant of the medium, the liquid-junction potential (which may give rise to errors of approximately 1 pH unit), and the hydrogen-ion response of the glass electrode are all changed. For these reasons, the values so obtained with solutions that are only partially aqueous in character can be regarded only as apparent pH values. However, acidity may be accurately measured with the proper use of electrodes and instrument standardization.

Buffer Solutions for Standardization of the pH Meter—

Buffer Solutions for Standardization are to be prepared as directed in the accompanying table. Buffer salts of requisite purity can be obtained from the National Bureau of Standards. Solutions may be stored in bottles of Type I glass. Fresh solutions should be prepared at intervals not to exceed 3 months. The table indicates the pH of the buffer solutions as a function of temperature. The instructions presented here are for the preparation of solutions having the designated molal (*m*) concentrations. For convenience, and to facilitate their preparation, however, instructions are given in terms of dilution to a 1000-ml volume rather than specifying the use of 1000 g of solvent, which is the basis of the molality system of solution concentration. The indicated quantities cannot be computed simply without additional information.

Potassium Tetraoxalate, 0.05 *m*—Dissolve 12.61 g of $KH_3(C_2O_4)_2 \cdot 2H_2O$ in water to make 1000 ml.

Potassium Biphthalate, 0.05 *m*—Dissolve 10.12 g of $KHC_8H_4O_4$, previously dried at 110° for 1 hour, in water to make 1000 ml.

Equimolal Phosphate, 0.05 *m*—Dissolve 3.53 g of Na_2HPO_4 and 3.39 g of KH_2PO_4, each previously dried at 120° for 2 hours, in water to make 1000 ml.

Sodium Tetraborate, 0.01 *m*—Dissolve 3.80 g of $Na_2B_4O_7 \cdot 10H_2O$ in water to make 1000 ml. Protect from absorption of carbon dioxide.

Calcium Hydroxide, saturated at 25°—Shake an excess of calcium hydroxide with water, and decant at 25° before use. Protect from absorption of carbon dioxide.

Because of variations in the nature and operation of the available pH meters, it is not practicable to give universally applicable directions for the potentiometric determinations of pH. The general principles to be followed in carrying out the instructions provided for each instrument by its manufacturer are set forth in the following paragraphs. Examine the electrodes and, if present, the salt bridge prior to use. If necessary, replenish the salt bridge solution, and observe other precautions indicated by the instrument or electrode manufacturer.

To standardize the pH meter, select two *Buffer Solutions for*

pH Values of Buffer Solutions for Standardization

Temperature, °C	Potassium Tetraoxalate, 0.05 *m*	Potassium Biphthalate, 0.05 *m*	Equimolal Phosphate, 0.05 *m*	Sodium Tetraborate, 0.01 *m*	Calcium Hydroxide, Saturated at 25°
10	1.67	4.00	6.92	9.33	13.00
15	1.67	4.00	6.90	9.28	12.81
20	1.67	4.00	6.88	9.23	12.63
25	1.68	4.01	6.86	9.18	12.45
30	1.68	4.02	6.85	9.14	12.29
35	1.68	4.02	6.84	9.10	12.13
40	1.69	4.04	6.84	9.07	11.98
45	1.69	4.05	6.83	9.04	11.84
50	1.70	4.06	6.83	9.01	11.71
55	1.71	4.08	6.84	8.99	11.57
60	1.72	4.09		8.96	11.45
	1.72				

...exceed 4 units and ... pH of the material under test falls between ... the cell with one of the *Buffer Solutions for Standardization* at the temperature at which the test material is to be ... Set the "temperature" control at the temperature of ... and adjust the calibration control to make the observed ... identical with that tabulated. Rinse the electrodes and ... portions of the second *Buffer Solution for Standardization*, then fill the cell with it, at the same temperature as the ... is measured. The pH of the second buffer solution is ... 0.07 pH unit of the tabulated value. If a larger deviation ... examine the electrodes and, if they are faulty, replace them. ... the "slope" or "temperature" control to make the observed ... identical with that tabulated. Repeat the standardization ... both *Buffer Solutions for Standardization* give observed pH ... within 0.02 pH unit of the tabulated value without further ... ment of the controls. When the system is functioning satisfactorily, rinse the electrodes and cell several times with a few ... of the test material, fill the cell with the test material, and ... the pH value. Use carbon dioxide–free water (see *Water*, in ... *Reagents, Indicators, and Solutions*) for solution or ... of test material in pH determinations.

... approximate pH values suffice, indicators and test papers ... *Indicators and Indicator Test Papers*, in the section, *Reagents, Indicators, and Solutions*) may be suitable.

... discussion of buffers, and for the composition of standard ... called for in compendial tests and assays, see *Buffer Solutions*, in the section, *Reagents, Indicators, and Solutions*.

⟨801⟩ POLAROGRAPHY

Polarography is an electrochemical method of analysis based on ... measurement of the current flow resulting from the electrolysis ... solution at a polarizable microelectrode, as a function of an ... applied voltage. The polarogram (see Figure 1) obtained by this ... measurement provides qualitative and quantitative information on ... the reducible and electro-oxidizable substances. The normal ... concentration range for substances being analyzed is from 10^{-2} ... 10^{-5} molar.

... direct current (dc) polarography, the microelectrode is a ... of mercury electrode (DME) consisting of small reproducible ... of mercury flowing from the orifice of a capillary tube con... to a mercury reservoir. A saturated calomel electrode ... with a large surface area is the most commonly employed ... reference electrode. As the voltage applied to the cell increases, ... very small residual current flows until the substance under ... undergoes reduction or oxidation. Then the current increases, ... gradually, then almost linearly with voltage, and it gradually ... a limiting value as is shown in Figure 1. On the initial rising ... of the polarographic wave, the increased flow of current ... a decrease in the concentration of the electro-active species ... electrode surface. As the voltage and current increase, the ... ration of the reactive species decreases further to a minimal ... at which the reacting species can diffuse from the bulk of the ... and by the surface of the microelectrode. The final current rise ... tration of reaction of the supporting electrolyte. This large ... electrolysis, and it prevents the reactive species from reaching ... by electrical migration, thus assuring that the limiting ... is diffusion-controlled.

... case of the DME, the electrode surface is being ... renewed in a cyclic fashion, the current increases from ... value as the drop begins to form to a maximum value as the ... drop is at the point of falling. By the use of a suitable recorder to measure the current, ... characteristic saw-toothed record is obtained. The limiting ... in the sum of the residual and the diffusion currents. The ... current is subtracted from the limiting current to give the ... height.

... Equation—The linear relationship between the diffusion ... and the concentration of electro-active species is shown ... Ilkovic equation,

$$i_d = 708nD^{1/2}Cm^{2/3}t^{1/6},$$

... i_d is the maximum current in microamperes, n is the ... of electrons required per molecule of electro-active sub... D is its diffusion coefficient, in square cm per second, C is

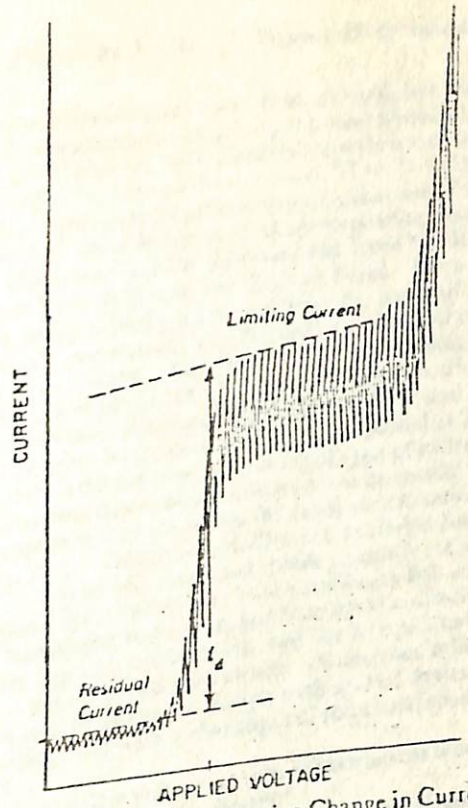


Fig. 1. Typical Polarogram Showing Change in Current Flow with Increasing Potential Applied to the Dropping Mercury Electrode.

the concentration, in millimoles per liter, m is the rate of mercury flow from the DME, in mg per second, and t is the drop time, in seconds.

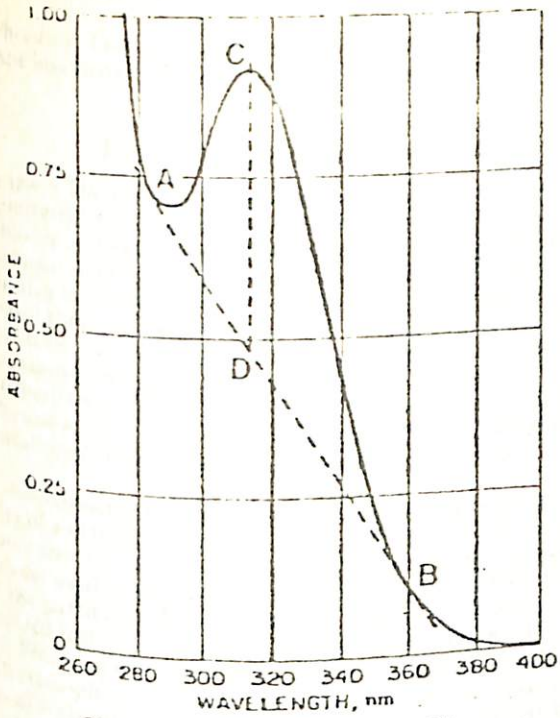
Modern polarographs are equipped with recorders capable of following the current during the latter portion of the drop life; consequently, the maximum of the oscillations is the measure of the current. When the current is measured only at the end of the drop life, the technique is termed sampled dc polarography. In this case, only the maximum currents are recorded and oscillations due to drop growth are not observed.

For instruments equipped with galvanometers to measure the current or recorders operated in a damped mode, the saw-toothed waves correspond to oscillations about the average current. In the latter case, the average of the oscillations is the measure of the current. For polarograms obtained in this manner, the i_d given by the Ilkovic equation is the average current in microamperes observed during the life of the drop, when the coefficient 708 is replaced by 607.

Control of the Diffusion Current—The Ilkovic equation identifies the variables that must be controlled to ensure that the diffusion current is directly proportional to the concentration of electro-active material. At 25° the diffusion coefficients for aqueous solutions of many ions and organic molecules increase 1% to 2% per degree rise in temperature. Thus the temperature of the polarographic cell must be controlled to within ±0.5°. The quantities m and t depend upon the dimensions of the capillary and the height of the mercury column above the electrode. Although results obtained with different capillaries can be compared if the product $m^{2/3}t^{1/6}$ is known, it is advisable to use the same capillary with a constant head of mercury during a series of analyses. The diffusion current is proportional to the square root of the height of the mercury column. A mercury reservoir with a diameter greater than 4 cm prevents any significant drop in the mercury level during a series of runs.

The capillary for the DME has a bore of approximately 0.04 mm and a length of 6 cm to 15 cm. The height of the mercury column, measured from the tip of the capillary to the top of the mercury pool, ranges from 40 cm to 80 cm. The exact length of the capillary and the height of the mercury column are adjusted to give a drop-time of between 3 and 5 seconds at open circuit with the capillary immersed in the test solution.

Equipment is available that allows controlled drop-times of fractions of a second to several seconds. As detail within a polar-



Typical Spectrum of Lemon Oil

against wavelength on the abscissa, and draw the absorption spectrum or spectrogram. Draw a base-line tangent to the latter, as shown in the accompanying figure (which is typical of Lemon Oil), between points *A* and *B*. Locate the point of maximum absorbance (*C*), and from it drop a vertical line, perpendicular to the abscissa, that intersects line *AB* at *D*. Read from the ordinate the absorbances corresponding to points *D* and *C*, subtract the former from the latter, and calculate the difference on the basis of a 250-mg sample.

⟨911⟩ VISCOSITY

Viscosity is a property of liquids that is closely related to the resistance to flow. It is defined in terms of the force required to move a plane surface continuously past another under specified steady-state conditions when the space between is filled by the liquid in question. It is defined as the shear stress divided by the rate of shear strain. The basic unit is the *poise*; however, viscosities commonly encountered represent fractions of the poise, so that the *centipoise* (1 poise = 100 centipoises) proves to be the more convenient unit. The specifying of temperature is important because viscosity changes with temperature; in general, viscosity decreases as temperature is raised. While on the absolute scale viscosity is measured in poises or centipoises, for convenience the kinematic scale, in which the units are *stokes* and *centistokes* (1 stoke = 100 centistokes) commonly is used. To obtain the kinematic viscosity from the absolute viscosity, the latter is divided by the density of the liquid at the same temperature, i.e., kinematic viscosity = (absolute viscosity)/(density). The sizes of the units are such that viscosities in the ordinary ranges are conveniently expressed in centistokes. The approximate viscosity in centistokes at room temperature of either is 0.2; of water, 1; of kerosene, 2.5; of mineral oil, 20 to 70; and of honey, 10,000.

Absolute viscosity can be measured directly if accurate dimensions of the measuring instruments are known, but it is more common practice to calibrate the instrument with a liquid of known viscosity and to determine the viscosity of the unknown fluid by comparison with that of the known.

Many substances, such as the gums employed in pharmacy, have variable viscosity, and most of them are less resistant to flow at higher flow rates. In such cases, a given set of conditions is selected for measurement, and the measurement obtained is considered to be an apparent viscosity. Since a change in the conditions of measurement would yield a different value for the apparent viscosity of such substances, the instrument dimensions and conditions for the measurement must be closely adhered to by the operator.

Measurement of Viscosity— The usual method for measurement of viscosity involves the determination of the time required for a definite volume of liquid to flow through a capillary. Many capillary-tube viscosimeters have been devised, but Ostwald and Ubbelohde viscosimeters are among the most frequently used. Several types are described, with directions for their use, by the American Society for Testing and Materials (ASTM, D-445). The viscosity of oils is expressed on arbitrary scales that vary from one country to another, there being several corresponding instruments. The most widely used are the Redwood No. I and No. II, the Engler, the Saybolt Universal, and the Saybolt Furol. Each of these instruments uses arbitrary units that bear the name of the instrument. Standard temperatures are adopted as a matter of convenience with these instruments. For the Saybolt instruments, measurements usually are made at 100°F and 210°F; Redwood instruments may be used at several temperatures up to 250°F; and values obtained on the Engler instrument usually are reported at 20°C and 50°C. A particularly convenient and rapid type of instrument is a rotational viscosimeter, which utilizes a bob or spindle immersed in the test specimen and measures the resistance to movement of the rotating part. Different spindles are available for given viscosity ranges, and several rotational speeds generally are available. Other rotational instruments may have a stationary bob and a rotating cup. The Brookfield, Rotovisco, and Stormer viscosimeters are examples of rotating-bob instruments, and the MacMichael is an example of the rotating-cup instrument. Numerous other rotational instruments of advanced design with special devices for reading or recording, and with wide ranges of rotational speed, have been devised.

Where only a particular type of instrument is suitable, the individual monograph so indicates.

For measurement of viscosity or apparent viscosity, the temperature of the substance being measured must be accurately controlled, since small temperature changes may lead to marked changes in viscosity. For usual pharmaceutical purposes, the temperature should be held to within ±0.1°.

Procedure for Cellulose Derivatives— Measurement of the viscosity of solutions of the high-viscosity types of methylcellulose is a special case, since they are too viscous for the commonly available viscosimeters. The Ubbelohde viscosimeter may be adapted (cf. ASTM, D-1347) to the measurement of the ranges of viscosity encountered in methylcellulose solutions.

Calibration of the Ostwald-Type Viscosimeter— Determine the viscosimeter constant, *k*, for each viscosimeter by the use of an oil of known viscosity.* Place a quantity of the oil (adjusted to 20.0 ± 0.1°) in the filling tube, and transfer it to the orifice tube by gentle suction, taking care to prevent bubble formation in the liquid by keeping the air vent tube closed. Adjust the meniscus of the column of liquid in the orifice tube to the level of the top graduation line. Open both the vent and orifice tubes in order to permit the liquid to flow into the reservoir against atmospheric pressure. (Failure to open the vent tube before releasing the orifice tube will yield false values.) Record the time in seconds for the liquid to flow from the upper mark to the lower mark in the orifice tube.

Calculate the viscosimeter constant, *k*, from the equation $k = v/dt$, in which *v* is the known viscosity of the liquid in centipoises, *d* is the specific gravity of the liquid tested at 20°/20°, and *t* is the time in seconds for the liquid to pass from the upper mark to the lower mark.

If a viscosimeter is repaired, it must be recalibrated, since even minor repairs frequently cause significant changes in the value of its constant, *k*.

⟨921⟩ WATER DETERMINATION

Many Pharmacopeial articles either are hydrates or contain water in adsorbed form. As a result, the determination of the water content is important in demonstrating compliance with the Pharmacopeial standards. Generally one of the methods given below is called for in the individual monograph, depending upon the nature of the article. Methods IV and V are for use on gases, and only if specified in the individual monographs. In rare cases, a choice is allowed between two methods. When the article contains water of hydration, the Titrimetric Method, the Azeotropic Method, or

* Oils of known viscosities may be obtained from the Cannon Instrument Co., Box 16, State College, Pa. 16801. For methylcellulose, choose an oil the viscosity of which is as close as possible

the Gravimetric Method is employed, as directed in the individual monograph, and the requirement is given under the heading, *Water*.

The heading, *Loss on drying* (see ⟨731⟩), is used in those cases where the loss sustained on heating may be not entirely water.

I—Titrimetric Method

Principle—The titrimetric determination of water is based upon the quantitative reaction of water with an anhydrous solution of sulfur dioxide and iodine dissolved in pyridine and an alcohol. The test specimen may be titrated with the *Reagent* directly, or the analysis may be carried out by a residual titration procedure. In the residual titration, excess *Reagent* is added to the test specimen, sufficient time is allowed for the reaction to reach completion, and the unconsumed *Reagent* is titrated with a standard solution of water in methanol. The residual titration procedure is applicable generally and avoids the difficulties that may be encountered in the direct titration of substances from which the bound water is released slowly.

The stoichiometry of the reaction is not exact, and the reproducibility of a determination depends upon such factors as the relative concentrations of the *Reagent* ingredients, the nature of the inert solvent used to dissolve the test specimen, and the technique used in the particular determination. Therefore, an empirically standardized technique is used in order to achieve the desired accuracy. Precision in the method is governed largely by the extent to which atmospheric moisture is excluded from the system. The titration of water is usually carried out with the use of anhydrous methanol as the solvent for the test specimen; however, other suitable solvents may be used for special or unusual test specimens.

Apparatus—Any apparatus may be used that provides for adequate exclusion of atmospheric moisture and determination of the end-point. In the case of a colorless solution that is titrated directly, the end-point may be observed visually as a change in color from canary yellow to amber. The reverse is observed in the case of a test specimen that is titrated residually. More commonly, however, the end-point is determined electrometrically with an apparatus employing a simple electrical circuit that serves to impress about 200 mv of applied potential between a pair of platinum electrodes (about 5 square mm in area and about 2.5 cm apart) immersed in the solution to be titrated. At the end-point of the titration a slight excess of the reagent increases the flow of current to between 50 and 150 microamperes for 30 seconds to 30 minutes, depending upon the solution being titrated. The time is shortest for substances that dissolve in the reagent. With some automatic titrators, the abrupt change in current or potential at the end-point serves to close a solenoid-operated valve that controls the buret delivering the titrant. Commercially available apparatus generally comprises a closed system consisting of one or two automatic burets and a tightly covered titration vessel fitted with the necessary electrodes and a magnetic stirrer. The air in the system is kept dry with a suitable desiccant such as phosphorus pentoxide, and the titration vessel may be purged by means of a stream of dry nitrogen or current of dry air.

Reagent—Add 125 g of iodine to a solution containing 670 ml of methanol and 170 ml of pyridine, and cool. Place 100 ml of pyridine in a 250-ml graduated cylinder and, keeping the pyridine cold in an ice bath, pass in dry sulfur dioxide until the volume reaches 200 ml. Slowly add this solution, with shaking, to the cooled iodine mixture. Shake well to dissolve the iodine, transfer the solution to the apparatus, and allow to stand overnight before standardizing. One ml of this solution when freshly prepared is equivalent to approximately 5 mg of water, but it deteriorates gradually; therefore, standardize it within 1 hour before use, or daily if in continuous use. Protect from light while in use. Store any bulk stock of the reagent in a suitably sealed, glass-stoppered container, fully protected from light, and under refrigeration. A commercially available, stabilized solution of Karl Fischer reagent may be used. The diluted *Reagent* called for in some monographs should be diluted as directed by the manufacturer. Either methanol or other suitable solvent, such as ethylene glycol monomethyl ether, may be used as the diluent.

Standardization of the Reagent—Place enough methanol in the titration vessel to cover the electrodes, and add sufficient *Reagent* to give the characteristic end-point color, or 100 ± 50 microamperes of direct current at about 200 mv of applied potential.

For determination of trace amounts of water (less than 1%), sodium tartrate may be used as a convenient water reference substance. Quickly add 150 to 350 mg of sodium tartrate ($C_4H_4Na_2O_6 \cdot 2H_2O$), accurately weighed by difference, and titrate to the end-point. The water equivalence factor F, in mg of water per ml of reagent, is given by the formula $2(18.02/230.08)(W/V)$, in which 18.02 and 230.08 are the molecular weights of water and sodium tartrate dihydrate, respectively. W is the weight, in mg, of sodium tartrate dihydrate, and V is the volume, in ml, of the *Reagent* consumed in the second titration.

For the precise determination of significant amounts of water (more than 1%), use purified water obtained by distillation as the reference substance. Quickly add between 25 mg and 250 mg of water, accurately weighed by difference, from a weighing pipet or from a pre-calibrated syringe or micropipet, the amount taken being governed by the reagent strength and the buret size, as referred to under *Volumetric Apparatus* ⟨31⟩. Titrate to the end-point. Calculate the water equivalence factor, F, in mg of water per ml of reagent, by the formula W/V, in which W is the weight, in mg, of the water, and V is the volume, in ml, of the reagent required.

Standardization of Aqueous Methanol for Residual Titration—Prepare a *Water-Methanol Solution* by diluting 2 ml of water with methanol to 1000 ml. Standardize this solution by titrating 25.0 ml with the *Reagent*, previously standardized as directed under *Standardization of the Reagent*. Calculate the water content, in mg per ml, of the *Water-Methanol Solution* by the formula $V'F/25$, in which V' is the volume of the *Reagent* consumed, and F is the water equivalence factor of the *Reagent*. Determine the water content of the *Water-Methanol Solution* weekly, and standardize the *Reagent* against it periodically as needed.

Procedure—Determine the water by *Method Ia*, unless otherwise specified in the individual monograph.

Method Ia (*direct titration*)—Unless otherwise specified, transfer 35 to 40 ml of methanol to the titration vessel, and titrate with the *Reagent* to the electrometric or visual end-point to consume any moisture that may be present. (Disregard the volume consumed, since it does not enter into the calculations.) Quickly add an accurately weighed or measured amount of the specimen under test estimated to contain 10 to 250 mg of water, unless otherwise specified in the individual monograph, mix, and again titrate with the *Reagent* to the electrometric or visual end-point. Calculate the water content of the specimen, in mg, by the formula SF, in which S is the volume, in ml, of the *Reagent* consumed in the second titration, and F is the water equivalence factor of the *Reagent*.

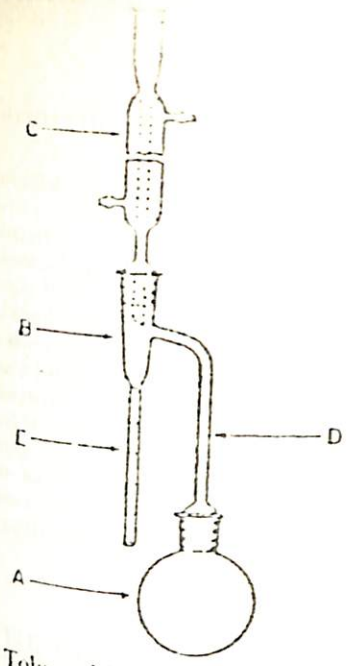
Method Ib (*residual titration*)—Where the individual monograph specifies that the water content is to be determined by *Method Ib*, the *residual titration* procedure, transfer 35 to 40 ml of methanol to the titration vessel, and titrate with the *Reagent* to the electrometric or visual end-point. Quickly add an accurately weighed or measured amount of the specimen under test estimated to contain 10 to 250 mg of water, mix, and add an accurately measured excess of the *Reagent*. Allow sufficient time for the reaction to reach completion, and titrate the unconsumed *Reagent* with standardized *Water-Methanol Solution* to the electrometric or visual end-point. Calculate the water content of the specimen, in mg, by the formula $F(X' - XR)$, in which F is the water equivalence factor of the *Reagent*, X' is the volume, in ml, of the *Reagent* added after introduction of the specimen, X is the volume, in ml, of standardized *Water-Methanol Solution* required to neutralize the unconsumed *Reagent*, and R is the ratio, $V'/25$ (ml *Reagent*/ml *Water-Methanol Solution*), determined from the *Standardization of Aqueous Methanol for Residual Titration*.

II—Azeotropic (Toluene Distillation) Method

Apparatus—Use a 500-ml glass flask *A* connected by means of a trap *B* to a reflux condenser *C* by ground glass joints (see illustration).

The critical dimensions of the parts of the apparatus are as follows: The connecting tube *D* is 9 to 11 mm in internal diameter. The trap is 235 to 240 mm in length. The condenser, if of the straight-tube type, is approximately 400 mm in length and not less than 8 mm in bore diameter. The receiving tube *E* has a 5-ml capacity and its cylindrical portion, 146 to 156 mm in length, is graduated in 0.1-ml subdivisions, so that the error of reading is not greater than 0.05 ml for any indicated volume. The source of heat is preferably an electric heater with rheostat control or an oil bath. The upper portion of the flask and the connecting tube may be insulated with asbestos.

Clean the receiving tube and the condenser with chromic acid cleansing mixture, thoroughly rinse with water, and dry in an oven.



Toluene Moisture Apparatus

...e the toluene to be used by first shaking with a small quantity ...ter, separating the excess water, and distilling the toluene.

...dure—Place in the dry flask a quantity of the substance, ...ected accurately to the nearest centigram, which is expected to ...to 4 ml of water. If the substance is of a pasty character, ...in a boat of metal foil of a size that will just pass through ...of the flask. If the substance is likely to cause bumping, ...enough dry, washed sand to cover the bottom of the flask, or ...der of capillary melting-point tubes, about 100 mm in length, ...at the upper end. Place about 200 ml of toluene in the flask, ...the apparatus, and fill the receiving tube *E* with toluene ...through the top of the condenser. Heat the flask gently for ...minutes and, when the toluene begins to boil, distil at the rate ...2 drops per second until most of the water has passed over, ...crease the rate of distillation to about 4 drops per second. ...the water has apparently all distilled over, rinse the inside ...condenser tube with toluene while brushing down the tube ...tube brush attached to a copper wire and saturated with ...Continue the distillation for 5 minutes, then remove the ...allow the receiving tube to cool to room temperature. If ...lets of water adhere to the walls of the receiving tube, scrub ...down with a brush consisting of a rubber band wrapped around ...wire and wetted with toluene. When the water and toluene ...arated completely, read the volume of water, and calculate ...ntage that was present in the substance.

III—Gravimetric Method

...dure for Chemicals—Proceed as directed in the individual ...with preparing the chemical as directed under *Loss on Drying* ...h.

...dure for Biologics—Proceed as directed in the individual ...g as directed (see (561)) and accurately weighed, in a tared ...ng dish. Dry at 105° for 5 hours, and weigh. Continue ...g and weighing at 1-hour intervals until the difference ...two successive weighings corresponds to not more than

IV—Dew-point Method

...surement of relatively low concentrations of water in the ...e in a gas is possible through the application of the fact ...water forms a fog or mist when suddenly cooled under ad...pansion following release of compression. A determi...means of a suitable instrument, of the dew point leads ...a calculation of the water content of the gas.

...The apparatus[1] consists of a self-contained unit into ...gas specimen is introduced through metal tubing. The ...gas is compressed while under continuous observation in a lighted fog chamber. The temperature of the specimen is read while pressure is applied. In successive trials, the pressure is increased and released until the minimum pressure that just produces a fog upon sudden release is determined. This is the dew point, and by reference to calibration charts, the water content is calculated.

V—Electrolytic Hygrometer Method

For the measurement of lower concentrations of water in gas than can be attained by any of the foregoing methods, an application of the principle of selective electrolysis of the water and measurement of the current required therefor is useful. By this method, continuous and quantitative absorption of the water from the gas stream is accompanied by subsequent electrolysis.

Apparatus—A suitable electrolytic hygrometer[2] is a self-contained unit that incorporates a sensor cell for the water absorption and electrolysis and a microammeter for measurement of the electric current required. The gas specimen is introduced into the unit through metal tubing and the water content is calculated or obtained by direct reading from the instrument.

⟨931⟩ WEIGHT VARIATION

The following tests provide limits for the permissible variations in the weights of individual dosage units, expressed in terms of the allowable deviation from the average weight of a sample. Separate procedures and limits are described herein for capsules; creams, ointments, and powders; sterile solids; and uncoated tablets.

For sterile solids with dry added substances, the content is determined separately by assay (see *Content Uniformity* ⟨681⟩).

Capsules

Capsules meet the requirements of the following test with respect to variation in weight of contents.

HARD CAPSULES

Weigh 20 intact capsules individually, and determine the average weight. The requirements are met if each of the individual weights is within the limits of 90% and 110% of the average weight.

If not all of the capsules fall within the aforementioned limits, weigh the 20 capsules individually, taking care to preserve the identity of each capsule, and remove the contents of each capsule with the aid of a small brush or pledget of cotton. Weigh the emptied shells individually, and calculate for each capsule the net weight of its contents by subtracting the weight of the shell from the respective gross weight. Determine the average net content from the sum of the individual net weights. Then determine the difference between each individual net content and the average net content: the requirements are met if (a) not more than 2 of the differences are greater than 10% of the average net content and (b) in no case is the difference greater than 25%.

If more than 2 but not more than 6 capsules deviate from the average between 10% and 25% determine the net contents of an additional 40 capsules, and determine the average content of the entire 60 capsules. Determine the 60 deviations from the new average: the requirements are met if (a) in not more than 6 of the capsules does the difference exceed 10% of the average net content and (b) in no case does the difference exceed 25%.

SOFT CAPSULES

Proceed as directed under *Hard Capsules*, but determine the net weight of the contents of individual capsules as follows: Weigh the intact capsules individually to obtain their gross weights, taking care to preserve the identity of each capsule. Then cut open the capsules by means of a suitable clean, dry cutting instrument such as scissors or a sharp open blade, and remove the contents by washing with a suitable solvent. Allow the occluded solvent to evaporate from the shells at room temperature over a period of about 30 minutes, taking precautions to avoid uptake or loss of moisture. Weigh the individual shells, and calculate the net contents. The requirements are as stated under *Hard Capsules*.

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[1] A suitable apparatus is available from Alnor Instrument Co. ...Testing Laboratories, Inc., 420 North La Salle St., ...60610.

[2] A suitable apparatus is available from several sources, including Bell and Howell Co. Electronics & Instruments Group, 360 Sierra Madre Villa, Pasadena, Calif. 91109; Process Instruments Div., Beckman Instruments, Inc., 2500 Harbor Blvd., Fullerton, Calif. 92634; and Manufacturer's Engineering & Equipment Corp., Sunset Lane, Hatboro, Pa 19040.

dose of the standard are uniform and between 20 and 70 mm of mercury, and are significantly less than the response to the larger dose of the standard.

Follow the time schedule established during the injection of the standard. Inject alternately a series of five doses consisting of the selected dose of the *Standard Preparation* and an equal-volume dose of the suitably diluted specimen under test. Measure the change in blood pressure following each of the five injections. Calculate the difference between each response to the dose of the test specimen and the mean of the associated doses of the *Standard Preparation* that immediately precede and follow it. The average of the differences is such that the response to the dilution of the test specimen is not greater than that of the dilution of the *Standard Preparation*, and the result corresponds to the limit on pressor activity specified for this test.

⟨141⟩ PROTEIN—BIOLOGICAL ADEQUACY TEST

This test is intended for the evaluation of the biological adequacy, as an index to the completeness of the mixture of amino acids contained, of Protein Hydrolysate Injection.

Depletion Diet—

	Parts by Weight
Dextrin	83.9
Corn Oil	9.0
Salt Mixture	4.0
Agar	2.0
Cod Liver Oil	1.0
Choline Chloride	0.15
Inositol	0.10
Calcium Pantothenate	0.002
Nicotinamide	0.0015
Riboflavin	0.0003
Pyridoxine	0.00025
Thiamine	0.0002
p-Aminobenzoic Acid	0.0002
Folic Acid	0.0002
Menadione	0.0002
Biotin	0.00002

Salt Mixture—Prepare the salt mixture specified in the *Depletion Diet* as follows:

Sodium Chloride	139.3 g
Potassium Biphosphate	389.0 g
Magnesium Sulfate, Anhydrous	57.3 g
Calcium Carbonate	381.4 g
Ferrous Sulfate	27.0 g
Manganese Sulfate	4.01 g
Potassium Iodide	0.79 g
Zinc Sulfate	0.548 g
Cupric Sulfate	0.477 g
Cobaltous Chloride	0.023 g

Place a portion of the weighed quantity of sodium chloride in a suitable mortar and add, with grinding, the potassium iodide. Set aside the mixture, and mix in a similar manner all the other salts with the remainder of the sodium chloride, adding finally the previously mixed sodium chloride and potassium iodide. Reduce the entire mixture to a fine powder (see *Powder Fineness* ⟨811⟩).

Nitrogen Supplement Mixture—Place 50 g of calcium caseinate and 46 g of anhydrous dextrose in a beaker, add sufficient water to make a paste, and finally add 1000 ml of water. Heat the mixture to between 70° and 82° for 5 minutes with stirring, and cool. Determine nitrogen on an aliquot using *Nitrogen Determination, Method I* or *Method II* ⟨461⟩. Store in a refrigerator. Mix before removing portions for analysis or use.

Depletion and Control Periods—Select a group of not less than 40 male rats 2 to 4 months of age and each weighing between 190 and 225 g. Place the rats in individual cages with free access to the *Depletion Diet* for 12 days. Weigh the depleted rats, and discard any rat that weighs more than 90% of its starting weight since the previous weighing.

Procedure—Assemble not less than six rats that have completed the depletion and control periods. For 5 days maintain the assembled rats on the *Depletion Diet* with a daily supplement of 20 ml, accurately measured, of a solution containing the Protein Hydrolysate Injection in an amount equivalent to 0.12 g of nitrogen offered each morning in the same way as the *Control Nitrogen Supplement Mixture* was offered previously. Withhold water for at least 2 hours prior to offering the supplement and for 4 hours afterward. Then if the supplement has been consumed, offer water ad libitum.

On the afternoon of the fifth day, weigh each rat, and compare the respective final and starting weights. Not fewer than 80% of the group of rats used gain weight or maintain their weight during the test.

⟨151⟩ PYROGEN TEST

The pyrogen test is designed to limit to an acceptable level the risks of febrile reaction in the patient to the administration, by injection, of the product concerned. The test involves measuring the rise in temperature of rabbits following the intravenous injection of a test solution and is designed for products that can be tolerated by the test rabbit in a dose not to exceed 10 ml per kg injected intravenously within a period of not more than 10 minutes. For products that require preliminary preparation or are subject to special conditions of administration, follow the additional directions given in the individual monograph or, in the case of antibiotics or biologics, the additional directions given in the federal regulations (see *Antibiotics* ⟨1011⟩, and *Biologics* ⟨1041⟩).

Apparatus and Diluents—Render the syringes, needles, and glassware free from pyrogens by heating at 250° for not less than 30 minutes or by any other suitable method. Treat all diluents and solutions for washing and rinsing of devices or parenteral injection assemblies in a manner that will assure that they are sterile and pyrogen-free. Periodically perform control pyrogen tests on representative portions of the diluents and solutions for washing or rinsing of the apparatus.

Temperature Recording—Use an accurate temperature-sensing device such as a clinical thermometer, or thermistor probes or similar probes that have been calibrated to assure an accuracy of ±0.1° and have been tested to determine that a maximum reading is reached in less than 5 minutes. Insert the temperature-sensing probe into the rectum of the test rabbit to a depth of not less than 7.5 cm, and, after a period of time not less than that previously determined as sufficient, record the rabbit's body temperature.

Test Animals—Use healthy, mature rabbits. House the rabbits individually in an area of uniform temperature between 20° and 23° and free from disturbances likely to excite them. The temperature varies not more than ±3° from the selected temperature. Before using a rabbit for the first time in a pyrogen test, condition it not more than seven days before use by a sham test that includes all of the steps as directed under *Procedure* except injection. Do not use a rabbit for pyrogen testing more frequently than once every 48 hours, nor prior to 2 weeks following a maximum rise of its temperature of 0.6° or more while being subjected to the pyrogen test, or following its having been given a test specimen that was adjudged pyrogenic.

Procedure—Perform the test in a separate area designated solely for pyrogen testing and under environmental conditions similar to those under which the animals are housed and free from disturbances likely to excite them. Withhold all food from the rabbits used during the period of the test. Access to water is allowed at all

...ed, to train the rabbits with light-fitting neck stocks that allow the rabbits to assume a natural resting posture. Not more than 30 minutes prior to the injection of the test dose, determine the "control temperature" of each rabbit: this is the base for the determination of any temperature increase resulting from the injection of a test solution. In any one group of test rabbits, use only those rabbits whose control temperatures do not vary by more than 1° from each other, and do not use any rabbit having a temperature exceeding 39.8°.

Unless otherwise specified in the individual monograph, inject into an ear vein of each of three rabbits 10 ml of the test solution per kg of body weight, completing each injection within 10 minutes after the start of administration. The test solution is *either* the product, reconstituted if necessary as directed in the labeling, *or* the material under test treated as directed in the individual monograph and injected in the dose specified therein. For pyrogen testing of devices such as injection assemblies, use washings or rinsings of the surfaces that come in contact with the parenterally administered material or with the injection site or internal tissues of the patient. Assure that all test solutions are protected from contamination. Perform the injection after warming the test solution to a temperature of 37 ± 2°. Record the temperature at 1, 2, and 3 hours subsequent to the injection.

Test Interpretation and Continuation—Consider any temperature decrease as zero rise. If no rabbit shows an individual rise in temperature of 0.6° or more above its respective control temperature, and if the sum of the three individual maximum temperature rises does not exceed 1.4°, the product meets the requirements for the absence of pyrogens. If any rabbit shows an individual temperature rise of 0.6° or more, or if the sum of the three individual maximum temperature rises exceeds 1.4°, continue the test using five other rabbits. If not more than three of the eight rabbits show individual rises in temperature of 0.6° or more, and if the sum of the eight individual maximum temperature rises does not exceed 3.7°, the material under examination meets the requirements for the absence of pyrogens.

RADIOACTIVE PHARMACEUTICALS

Test Dose for Preformulated, Ready-to-use Products Labeled with Radioactivity

AGGREGATED ALBUMIN AND OTHER PARTICLE-CONTAINING PRODUCTS

For the rabbit pyrogen test, dilute the product with Sodium Chloride Injection to not less than 100 μCi per ml, and inject a dose of 3 ml per kg of body weight into each rabbit.

OTHER PRODUCTS

Where Physical Half-life of Radionuclide is Greater Than 1 Day—Calculate the maximum volume of the product that might be injected into a human subject. This calculation takes into account the maximum recommended radioactive dose of the product, the μCi and the radioactive assay, in μCi per ml, of the product at the expiration date or time. Using this information, calculate the maximum volume dose per kg to a 70-kg human subject.

For the rabbit pyrogen test, inject a minimum of 10 times this dose per kg of body weight into each rabbit. If necessary, dilute with Sodium Chloride Injection. The total injected volume per rabbit is not less than 1 ml and not more than 10 ml of solution.

Where Physical Half-life or Radionuclide is Less Than 1 Day—For products labeled with radionuclides having a half-life of less than 1 day, the dosage calculations are identical to those described in the first paragraph under *Other Products*. These products may be released for distribution prior to completion of the rabbit pyrogen test, but such test shall be initiated at not more than 36 hours after release.

Test Dose for Pharmaceutical Constituents or Reagents to Be Labeled

The following test dose requirements pertain to reagents that are to be labeled or constituted prior to use by the direct addition of radioactive solutions such as Sodium Pertechnetate Tc 99m Injection, i.e., "cold kits." Assume that the entire contents of the vial of nonradioactive reagent will be injected into a 70-kg human subject or that 1/10 of the total contents per kg will be injected. If the contents are dry, constitute with a measured volume of Sodium Chloride Injection.

For the rabbit pyrogen test, inject 1/7 of the vial contents per kg of body weight into each rabbit. The maximum dose per rabbit is the entire contents of a single vial. The total injected volume per rabbit is not less than 1 ml and not more than 10 ml of solution.

⟨161⟩ TRANSFUSION AND INFUSION ASSEMBLIES

The following tests are provided for application to representative specimens of disposable transfusion and infusion assemblies of tubing.

Sterility—Proceed as directed for *Sterile Devices* under *Sterility Tests* ⟨71⟩.

Pyrogens—Select 10 assemblies representative of the production of each working day, and through the tubing of each pass a separate 40-ml portion of sterile, pyrogen-free saline TS at a flow rate of approximately 10 ml per minute. The pooled effluent meets the requirements of the *Pyrogen Test* ⟨151⟩, the test dose being 10 ml per kg of body weight.

Safety—Select 1 transfusion and infusion assembly representative of the production of each working day. Fill the assembly as completely as practicable with sterile saline TS, clamp the ends securely to retain the solution, and immerse the filled assembly completely in water. Heat the water at not less than 85° for 1 hour. Drain the contents of the assembly, and dilute with sterile saline TS to 250 ml. Inject intravenously 0.5 ml of the solution so prepared into each of five healthy mice weighing between 17 and 23 g: at the end of 4, 24, and 48 hours the animals show no discernible symptoms of toxicity: if any of the animals show gross signs of toxicity or die, repeat the test with another five healthy mice weighing 20 ± 1 g each: all of the animals survive for 48 hours.

Other requirements—Those parts of the assemblies that are made of plastic meet the requirements under *Containers* ⟨661⟩.

⟨171⟩ VITAMIN B_{12} ACTIVITY ASSAY

Reference Standard—*USP Cyanocobalamin Reference Standard*—Keep container tightly closed and protected from light. Dry over silica gel for 4 hours before using.

Assay Preparation—Place a suitable quantity of the material to be assayed, previously reduced to a fine powder if necessary and accurately measured or weighed, in an appropriate vessel containing, for each g or ml of material taken, 25 ml of an aqueous extracting solution prepared just prior to use to contain, in each 100 ml, 1.29 g of disodium phosphate, 1.1 g of anhydrous citric acid, and 1.0 g of sodium metabisulfite. Autoclave the mixture at 121° for 10 minutes. Allow any undissolved particles of the extract to settle, and filter or centrifuge, if necessary. Dilute an aliquot of the clear solution with water so that the final test solution contains vitamin B_{12} activity approximately equivalent to that of the *Standard Cyanocobalamin Solution* which is added to the assay tubes.

Standard Cyanocobalamin Stock Solution—To a suitable quantity of USP Cyanocobalamin RS, accurately weighed, add sufficient 25 percent alcohol to make a solution having a known concentration of 1.0 μg of cyanocobalamin per ml. Store in a refrigerator.

Standard Cyanocobalamin Solution—Dilute a suitable volume of *Standard Cyanocobalamin Stock Solution* with water to a measured volume such that after the incubation period as described under *Procedure*, the difference in transmittance between the inoculated blank and the 5.0-ml level of the *Standard Cyanocobalamin Solution* is not less than that which corresponds to a difference of 1.25 mg in dried cell weight. This concentration usually falls between 0.01 ng and 0.04 ng per ml of *Standard Cyanocobalamin Solution*. Prepare a fresh standard solution for each assay.

Basal Medium Stock Solution—Prepare the medium according to the following formula and directions. A dehydrated mixture containing the same ingredients may be used provided that, when constituted as directed in the labeling, it yields a medium comparable to that obtained from the formula given herein.

Add the ingredients in the order listed, carefully dissolving the cystine and tryptophane in the hydrochloric acid before adding the next eight solutions in the resulting solution. Add 100 ml of water, mix, and dissolve the dextrose, sodium acetate, and ascorbic acid. Filter, if necessary, add the polysorbate 80 solution, adjust the solution to a pH between 5.5 and 6.0 with 1 *N* sodium hydroxide, and add purified water to make 250 ml.

l-Cystine	0.1 g
l-Tryptophane	0.05 g
1 *N* Hydrochloric Acid	10 ml
Adenine-Guanine-Uracil Solution	5 ml
Xanthine Solution	5 ml
Vitamin Solution I	10 ml
Vitamin Solution II	10 ml
Salt Solution A	5 ml
Salt Solution B	5 ml
Asparagine Solution	5 ml
Acid-Hydrolyzed Casein Solution	25 ml
Dextrose, Anhydrous	10 g
Sodium Acetate, Anhydrous	5 g
Ascorbic Acid	1 g
Polysorbate 80 Solution	5 ml

Acid-Hydrolyzed Casein Solution—Prepare as directed under *Calcium Pantothenate Assay* ⟨91⟩.

Asparagine Solution—Dissolve 2.0 of *l*-asparagine in water to make 200 ml. Store under toluene in a refrigerator.

Adenine-Guanine-Uracil Solution—Prepare as directed under *Calcium Pantothenate Assay* ⟨91⟩.

Xanthine Solution—Suspend 0.20 g of xanthine in 30 ml to 40 ml of water, heat to about 70°, add 6.0 ml of 6 *N* ammonium hydroxide, and stir until the solid is dissolved. Cool, and add water to make 200 ml. Store under toluene in a refrigerator.

Salt Solution A—Dissolve 10 g of monobasic potassium phosphate and 10 g of dibasic potassium phosphate in water to make 200 ml. Add 2 drops of hydrochloric acid, and store under toluene.

Salt Solution B—Dissolve 4.0 g of magnesium sulfate, 0.20 g of sodium chloride, 0.20 g of ferrous sulfate, and 0.20 g of manganese sulfate in water to make 200 ml. Add 2 drops of hydrochloric acid, and store under toluene.

Polysorbate 80 Solution—Dissolve 20 g of polysorbate 80 in alcohol to make 200 ml. Store in a refrigerator.

Vitamin Solution I—Dissolve 10 mg of riboflavin, 10 mg of thiamine hydrochloride, 100 µg of biotin, and 20 mg of niacin in 0.02 *N* glacial acetic acid to make 400 ml. Store, protected from light, under toluene in a refrigerator.

Vitamin Solution II—Dissolve 20 mg of para-aminobenzoic acid, 40 mg of calcium pantothenate, 40 mg of pyridoxine hydrochloride, 40 mg of pyridoxal hydrochloride, 8 mg of pyridoxamine dihydrochloride, and 2 mg of folic acid in dilute neutralized alcohol (1 in 4) to make 400 ml. Store, protected from light, in a refrigerator.

Tomato Juice Preparation—Centrifuge commercially canned tomato juice so that most of the pulp is removed. Suspend about 5 g per liter of analytical filter-aid in the supernatant liquid, and filter, with the aid of reduced pressure, through a layer of the filter-aid. Repeat, if necessary, until a clear, straw-colored filtrate is obtained. Store under toluene in a refrigerator.

Culture Medium—[NOTE—A dehydrated mixture containing the same ingredients may be used provided that, when constituted as directed in the labeling, it yields a medium equivalent to that obtained from the formula given herein.] Dissolve 0.75 g of water-soluble yeast extract, 0.75 g of dried peptone, 1.0 g of anhydrous dextrose, and 0.20 g of potassium biphosphate in 60 ml to 70 ml of water. Add 10 ml of *Tomato Juice Preparation* and 1 ml of *Polysorbate 80 Solution*. Adjust the solution with 1 *N* sodium hydroxide to a pH of 6.8, and add water to make 100 ml. Place 10-ml portions of the solution in test tubes, and plug with cotton. Sterilize the tubes and contents in an autoclave at 121° for 15 minutes. Cool as rapidly as possible to avoid color formation resulting from overheating the medium.

Suspension Medium—Dilute a measured volume of *Basal Medium Stock Solution* with an equal volume of water. Place 10-ml portions of the diluted medium in test tubes. Sterilize, and cool as directed above for the *Culture Medium*.

Stock Culture of Lactobacillus leichmannii—To 100 ml of *Culture Medium* add 1.0 g to 1.5 g of agar, and heat the mixture, with stirring, on a steam bath, until the agar dissolves. Place approximately 10-ml portions of the hot solution in test tubes, cover the tubes suitably, sterilize at 121° for 15 minutes in an autoclave (exhaust line temperature), and allow the tubes to cool in an upright position. Inoculate three or more of the tubes, by stab transfer of a pure culture of *Lactobacillus leichmannii*.* (Before first using a fresh culture in this assay, make not fewer than 10 successive transfers of the culture in a 2-week period.) Incubate 16 to 24 hours at any selected temperature between 30° and 40° but held constant to within ±0.5°, and finally store in a refrigerator.

Prepare fresh stab cultures at least three times each week, and do not use them for preparing the inoculum if more than 4 days old. The activity of the microorganism can be increased by daily or twice-daily transfer of the stab culture, to the point where definite turbidity in the liquid inoculum can be observed 2 to 4 hours after inoculation. A slow-growing culture seldom gives a suitable response curve, and may lead to erratic results.

Inoculum—[NOTE—A frozen suspension of *Lactobacillus leichmannii* may be used as the stock culture, provided that it yields an inoculum comparable to a fresh culture.] Make a transfer of cells from the *Stock Culture of Lactobacillus leichmannii* to a sterile tube containing 10 ml of the *Culture Medium*. Incubate this culture for 6 to 24 hours at any selected temperature between 30° and 40° but held constant to within ±0.5°. Under aseptic conditions, centrifuge the culture, and decant the supernatant liquid. Suspend the cells from the culture in 10 ml of sterile suspension medium. Dilute an aliquot with sterile suspension medium to give a transmittance that corresponds to a cell weight (as described under *Procedure*) of 500 µg to 750 µg per tube when read against the suspension medium set at 100% transmittance.

Calibration of Spectrophotometer—Add aseptically 1.0 ml of *Inoculum* to 300 ml of suspension medium containing 500 µl of *Standard Cyanocobalamin Stock Solution*. Incubate the inoculated medium for the same period and at the same temperature to be employed in the assay procedure.

Following the incubation period, centrifuge and wash the cells three times with approximately 50-ml portions of saline TS, and then resuspend the cells in about 25 ml of saline TS.

Dry a 10-ml portion, accurately measured, to constant weight using a steam bath and completing the drying in vacuum at 100°, and calculate the dry weight of the cells, in mg per ml, corrected for the amount of sodium chloride present.

Dilute a second portion, accurately measured, of the saline cell suspension with saline TS so that each ml contains a known quantity of cells equivalent to about 500 µg on the dried basis. To test tubes add, in triplicate, 0.50 ml, 1.0 ml, 1.5 ml, 2.0 ml, 2.5 ml, 3.0 ml, 4.0 ml, and 5.0 ml, respectively, of this diluted cell suspension and 5.0 ml of *Basal Medium Stock Solution*, and make up the volume in each tube to 10.0 ml with saline TS. Using as the blanks three similar tubes containing no cell suspension, measure the light transmittance of each tube under the same conditions to be employed under *Procedure*. Plot the observations as the ordinate on cross-section paper against the cell content, expressed as mg of dry weight, as the abscissa.

Repeat the procedure at least twice for the spectrophotometer to be used in the assay. Draw the composite curve best representing the three or more individual curves relating transmittance to cell density for the spectrophotometer under the conditions of the assay.

Procedure—Cleanse meticulously by suitable means, followed preferably by heating at 250° for 2 hours, hard-glass test tubes, about 20 mm × 150 mm in size, and other necessary glassware because of the high sensitivity of the test organism to minute amounts of vitamin B_{12} activity and to traces of many cleansing agents.

To test tubes add, in duplicate, 1.0 ml, 1.5 ml, 2.0 ml, 3.0 ml, 4.0 ml, and 5.0 ml, respectively, of the *Standard Cyanocobalamin Solution*. To each of these tubes and to four similar empty tubes add 5.0 ml of *Basal Medium Stock Solution* and water to make 10 ml.

* Pure cultures of *Lactobacillus leichmannii* may be obtained as No. 7830 from the American Type Culture Collection, 12301 Parklawn Drive, Rockville, Md. 20852

...similar test tubes add, in duplicate, respectively, 1.0 ml, 1.5 ml, 2.0 ml, 3.0 ml, and 4.0 ml of the *Assay Preparation*. To each tube add 5.0 ml of *Basal Medium Stock Solution* and water to make 10 ml. Place one complete set of standard and assay tubes together in one tube rack and the duplicate set in a second rack or section of a rack, preferably in random order.

Cover the tubes suitably to prevent bacterial contamination, and sterilize the tubes and contents in an autoclave at 121° for 5 minutes, arranging to reach this temperature in not more than 10 minutes by preheating the autoclave, if necessary. Cool as rapidly as practicable to avoid color formation resulting from overheating the medium. Take precautions to maintain uniformity of sterilizing and cooling conditions throughout the assay, since packing tubes too closely in the autoclave, or overloading it, may cause variation in the heating rate.

Aseptically add 1 drop of *Inoculum* to each tube so prepared except two of the four containing no *Standard Cyanocobalamin Solution* (the uninoculated blanks). Incubate the tubes at a temperature between 30° and 40° held constant to within ±0.5°, until, following 16 or 24 hours of incubation, there has been no substantial increase in turbidity in the tubes containing the highest level of standard during a 2-hour period.

Determine the transmittance of the tubes in the following manner. Mix the contents of each tube, to which 1 drop of a suitable antifoam agent solution may be added, and transfer to a spectrophotometer cell. After agitating its contents, place the container in a spectrophotometer that has been set at any specific wavelength between 500 nm and 660 nm, and read the transmittance when a steady state is reached. This steady state is observed a few seconds after agitation when the reading remains constant for 30 seconds or more. Allow approximately the same time interval for the reading on each tube.

With the transmittance set at 1.00 for the uninoculated blank, read the transmittance of the inoculated blank. If this transmittance reading corresponds to a dried cell weight greater than 600 mcg per tube, or if there is evidence of contamination with a foreign microorganism, disregard the results of the assay.

With the transmittance set at 1.00 for the inoculated blank, read the transmittance for each of the remaining tubes. Disregard the results of the assay if the difference between the transmittance observed at the highest level of the standard and that of the inoculated blank is less than the difference corresponding to a dried cell weight of 1.25 mg per tube.

Calculation—Prepare a standard concentration–response curve by the following procedure. Test for and replace any aberrant individual transmittances. For each level of the standard, calculate the response from the sum of the duplicate values of the transmittances (Σ) as the difference, $y = 2.00 - \Sigma$. Plot this response on the ordinate of cross-section paper against the logarithm of the ml of *Standard Cyanocobalamin Solution* per tube on the abscissa, using for the ordinate either an arithmetic or a logarithmic scale, whichever gives the better approximation to a straight line. Draw a straight line or smooth curve that best fits the plotted points. Calculate the response, y, adding together the two transmittances for each level of the *Assay Preparation*. Read from the standard curve the logarithm of the volume of the *Standard Preparation* corresponding to each of those values of y that falls within the range of the lowest and highest points plotted for the standard. Subtract each logarithm so obtained the logarithm of the volume, in ml, of *Assay Preparation* to obtain the difference, x, for each dosage level. Average the values of x for each of three or more dosage levels to obtain $\bar{x} = M'$, the log-relative potency of the *Assay Preparation* RS. Determine the quantity, in μg, of USP Cyanocobalamin RS corresponding to the cyanocobalamin in the portion of material taken for assay by the equation antilog M = antilog (M' + R), in which R is the number of μg of cyanocobalamin that is assumed to be present in each mg (or capsule or tablet) of the material taken for assay.

Replication—Repeat the entire determination at least once, using freshly prepared *Assay Preparations*. If the difference between the two log potencies M is not greater than 0.08, their mean, $\overline{M}$, is the log potency of the test material (see *Vitamin B_{12} Activity Assay* under *Design and Analysis of Biological Assays*). If the two determinations differ by more than 0.08, conduct one or more additional determinations. From the mean of two mean values of M that do not differ by more than 0.15, compute the potency of the preparation under assay.

Chemical Tests and Assays

IDENTIFICATION TESTS

⟨181⟩ IDENTIFICATION—ORGANIC NITROGENOUS BASES

Dissolve 50 mg of the specified salt of the organic nitrogenous base, if in bulk, in 25 ml of water, or shake a quantity of powdered tablets or the contents of capsules equivalent to 50 mg of the salt with 25 ml of 0.01 *N* hydrochloric acid for 10 minutes. Transfer the liquid to a separator, if necessary filtering it and washing the filter and the residue with several small portions of water. In a second separator dissolve 50 mg of the corresponding USP Reference Standard in 25 ml of water. Treat each solution as follows: Add 2 ml of 1 *N* sodium hydroxide and 4 ml of carbon disulfide, and shake for 2 minutes. Centrifuge if necessary to clarify the lower phase, and filter it through a dry filter, collecting the filtrate in a small flask provided with a glass stopper.

Determine the absorption spectra of the filtered solutions of both standard and sample without delay, in 1-mm cells between 7 μm and 15 μm, with a suitable infrared spectrophotometer, using carbon disulfide in a matched cell as the blank. The spectrum of the solution prepared from the sample shows all of the significant absorption bands present in the spectrum of the solution prepared from the Reference Standard.

⟨191⟩ IDENTIFICATION TESTS—GENERAL

Under this heading are placed tests that are frequently referred to in the Pharmacopeia for the identification of official articles.

NOTE—The tests are not intended to be applicable to mixtures of substances unless so specified.

Acetate—When acetic acid or an acetate is warmed with sulfuric acid and alcohol, ethyl acetate, recognizable by its characteristic odor, is evolved. With neutral solutions of acetates, ferric chloride TS produces a deep red color which is destroyed by the addition of mineral acids.

Aluminum—Solutions of aluminum salts yield with 6 *N* ammonium hydroxide a gelatinous, white precipitate that is insoluble in an excess of 6 *N* ammonium hydroxide. 1 *N* sodium hydroxide or sodium sulfide TS produces the same precipitate, which dissolves in an excess of either of these reagents.

Ammonium—Ammonium salts are decomposed by the addition of an excess of 1 *N* sodium hydroxide, with the evolution of ammonia, recognizable by its odor and by its alkaline effect upon moistened red litmus paper exposed to the vapor. Warming the solution accelerates the decomposition.

Antimony—Solutions of antimony (III) compounds, strongly acidified with hydrochloric acid, yield with hydrogen sulfide an orange precipitate of antimony sulfide which is insoluble in 6 *N* ammonium hydroxide, but is soluble in ammonium sulfide TS.

Barium—Solutions of barium salts yield a white precipitate with 2 *N* sulfuric acid. This precipitate is insoluble in hydrochloric and in nitric acid. Barium salts impart a yellowish green color to a nonluminous flame, which appears blue when viewed through green glass.

Benzoate—In neutral solutions, benzoates yield a salmon-colored precipitate with ferric chloride TS. In moderately concentrated solutions, benzoates yield a precipitate of benzoic acid upon acidification with 2 *N* sulfuric acid. This precipitate is readily soluble in ether.

Bicarbonate—See *Carbonate*.

Bismuth—When dissolved in a slight excess of nitric or hydrochloric acid, bismuth salts yield a white precipitate upon dilution with water. This precipitate is colored brown by hydrogen sulfide, and the resulting compound dissolves in a warm mixture of equal parts of nitric acid and water.

Bisulfite—See *Sulfite*.

Borate—To 1 ml of a borate solution, acidified with hydrochloric acid to litmus, add 3 or 4 drops of iodine solution (1 in 1000) and 3 or 4 drops of polyvinyl alcohol solution (1 in 50): an intense blue color is produced. When a borate is treated with sulfuric acid, methanol is added, and the mixture is ignited, it burns with a green-bordered flame.

Bromide—Solutions of bromides, upon the addition of chlorine TS, dropwise, liberate bromine, which is dissolved by shaking with chloroform, coloring the chloroform red to reddish brown. Silver nitrate TS produces in solutions of bromides a yellowish white precipitate, which is insoluble in nitric acid and is slightly soluble in 6 *N* ammonium hydroxide.

Calcium—Solutions of calcium salts form insoluble oxalates when treated as follows: To a solution of the calcium salt (1 in 20) add 2 drops of methyl red TS, and neutralize with 6 *N* ammonium hydroxide. Add 3 *N* hydrochloric acid, dropwise, until the solution is acid to the indicator. Upon the addition of ammonium oxalate TS, a white precipitate is formed. This precipitate is insoluble in 6 *N* acetic acid but dissolves in hydrochloric acid. Calcium salts moistened with hydrochloric acid impart a transient yellowish red color to a nonluminous flame.

Carbonate—Carbonates and bicarbonates effervesce with acids, evolving a colorless gas, which when passed into calcium hydroxide TS produces a white precipitate immediately. A cold solution of a soluble carbonate is colored red by phenolphthalein TS, while a similar solution of a bicarbonate remains unchanged or is only slightly colored.

Chlorate—Solutions of chlorates yield no precipitate with silver nitrate TS. The addition of sulfurous acid to this mixture produces a white precipitate which is insoluble in nitric acid, but is soluble in 6 *N* ammonium hydroxide. Upon ignition, chlorates yield chlorides, recognizable by appropriate tests. When sulfuric acid is added to a dry chlorate, decrepitation occurs and a greenish yellow gas is evolved. (*Caution—Use only a small amount of chlorate for this test, and exercise extreme caution in performing it.*)

Chloride—Solutions of chlorides yield with silver nitrate TS a white, curdy precipitate, which is insoluble in nitric acid, but is soluble in a slight excess of 6 *N* ammonium hydroxide. When testing alkaloidal hydrochlorides, add 6 *N* ammonium hydroxide, filter, acidify the filtrate with nitric acid, and proceed as directed above. Dry chlorides, when mixed with an equal weight of manganese dioxide, moistened with sulfuric acid, and gently heated, evolve chlorine which is recognizable by its odor and by the production of a blue color with moistened starch iodide paper.

Citrate—Upon the addition of a few mg of a citrate to a mixture of 15 ml of pyridine and 5 ml of acetic anhydride, a carmine red color is produced.

Cobalt—Solutions of cobalt salts (1 in 20) in 3 *N* hydrochloric acid yield a red precipitate when heated on a steam bath with an equal volume of a hot, freshly prepared solution of 1-nitroso-2-naphthol (1 in 10) in 9 *N* acetic acid. Solutions of cobalt salts, when saturated with potassium chloride and treated with potassium nitrite and acetic acid, yield a yellow precipitate.

Copper—Solutions of cupric compounds, acidified with hydrochloric acid, deposit a red film of metallic copper upon a bright, unburnished surface of metallic iron. An excess of 6 *N* ammonium hydroxide, added to a solution of a cupric salt, produces first a bluish precipitate and then a deep blue-colored solution. With potassium ferrocyanide TS, solutions of cupric salts yield a reddish brown precipitate, insoluble in diluted acids.

Hypophosphite—When strongly heated, hypophosphites evolve spontaneously flammable phosphine. Hypophosphites in solution yield a white precipitate with mercuric chloride TS. This precipitate becomes gray when an excess of hypophosphite is present. Solutions of hypophosphites, acidified with sulfuric acid, and treated with cupric sulfate TS yield a red precipitate.

Iodide—Solutions of iodides, upon the addition of chlorine TS, liberate iodine, which colors the solution yellow to red. When the solution is shaken with chloroform, the latter is colored violet. The iodine thus liberated gives a blue color with starch TS. Silver nitrate TS produces in solutions of iodides a yellow, curdy precipitate, which is insoluble in nitric acid and in 6 *N* ammonium hydroxide.

Iron—Ferrous and ferric compounds in solution yield a black precipitate with ammonium sulfide TS. This precipitate is dissolved by cold 3 *N* hydrochloric acid with the evolution of hydrogen sulfide.

FERRIC SALTS—Acid solutions of ferric salts yield a dark blue precipitate with potassium ferrocyanide TS. With an excess of 1 *N* sodium hydroxide, a reddish brown precipitate is formed. Solutions of ferric salts produce with ammonium thiocyanate TS a deep red color which is not destroyed by dilute mineral acids.

FERROUS SALTS—Solutions of ferrous salts yield a dark blue precipitate with potassium ferricyanide TS. This precipitate is insoluble in 3 *N* hydrochloric acid, but is decomposed by 1 *N* sodium hydroxide. Solutions of ferrous salts yield with 1 *N* sodium hydroxide a greenish white precipitate, the color rapidly changing to green and then to brown when shaken.

Lactate—When solutions of lactates are acidified with sulfuric acid, potassium permanganate TS is added, and the mixture is heated, acetaldehyde, recognizable by its distinctive odor, is evolved.

Lead—Solutions of lead salts yield with 2 *N* sulfuric acid a white precipitate which is insoluble in 3 *N* hydrochloric or 2 *N* nitric acid, but is soluble in warm 1 *N* sodium hydroxide and in ammonium acetate TS. With potassium chromate TS, solutions of lead salts, free or nearly free from mineral acids, yield a yellow precipitate which is insoluble in 6 *N* acetic acid, but is soluble in 1 *N* sodium hydroxide.

Lithium—Moderately concentrated solutions of lithium salts, made alkaline with sodium hydroxide, yield with sodium carbonate TS a white precipitate on boiling. The precipitate is soluble in ammonium chloride TS. Lithium salts moistened with hydrochloric acid impart an intense crimson color to a nonluminous flame. Solutions of lithium salts are not precipitated by 2 *N* sulfuric acid or soluble sulfates (*distinction from strontium*).

Magnesium—Solutions of magnesium salts in the presence of ammonium chloride yield no precipitate with ammonium carbonate TS, but on the subsequent addition of sodium phosphate TS, a white, crystalline precipitate, which is insoluble in 6 *N* ammonium hydroxide, is formed.

Manganese—Solutions of manganous salts yield with ammonium sulfide TS a salmon-colored precipitate, which dissolves in acetic acid.

Mercury—Solutions of mercury salts, free from an excess of nitric acid, when applied to bright copper foil, yield a deposit, which, upon rubbing, becomes bright and silvery in appearance. With hydrogen sulfide, solutions of mercury compounds yield a black precipitate, which is insoluble in ammonium sulfide TS and in boiling 2 *N* nitric acid.

MERCURIC SALTS—Solutions of mercuric salts yield a yellow precipitate with 1 *N* sodium hydroxide. They yield also, in neutral solutions with potassium iodide TS, a scarlet precipitate, which is very soluble in an excess of the reagent.

MERCUROUS SALTS—Mercurous compounds are decomposed by 1 *N* sodium hydroxide, producing a black color. Solutions of mercurous salts yield with hydrochloric acid a white precipitate which is blackened by 6 *N* ammonium hydroxide. With potassium iodide TS, a yellow precipitate, which may become green upon standing, is formed.

Nitrate—When a solution of a nitrate is mixed with an equal volume of sulfuric acid, the mixture is cooled, and a solution of ferrous sulfate is superimposed, a brown color is produced at the junction of the two liquids. When a nitrate is heated with sulfuric acid and metallic copper, brownish red fumes are evolved. Nitrates do not decolorize acidified potassium permanganate TS (*distinction from nitrites*).

Nitrite—When treated with dilute mineral acids or with 6 *N* acetic acid, nitrites evolve brownish red fumes. The solution colors starch-iodide paper blue.

Oxalate—Neutral and alkaline solutions of oxalates yield a white precipitate with calcium chloride TS. This precipitate is insoluble in 6 *N* acetic acid, but is dissolved by hydrochloric acid. Hot acidified solutions of oxalates decolorize potassium permanganate TS.

Permanganate—Solutions of permanganates acidified with sulfuric acid are decolorized by hydrogen peroxide TS and by sodium bisulfite TS, in the cold, and by oxalic acid TS, in hot solution.

Peroxide—Solutions of peroxides slightly acidified with sulfuric

...and a deep blue color upon the addition of potassium dichromate TS. On shaking the mixture with an equal volume of ether and allowing the liquids to separate, the blue color is found in the ether layer.

Phosphate - Neutral solutions of orthophosphates yield with silver nitrate TS a yellow precipitate, which is soluble in 2 *N* nitric acid or in 6 *N* ammonium hydroxide. With ammonium molybdate TS a yellow precipitate, which is soluble in 6 *N* ammonium hydroxide is formed.

Potassium—Potassium compounds impart a violet color to a colorless flame, but the presence of small quantities of sodium masks the color. In neutral, concentrated or moderately concentrated solutions of potassium salts (depending upon the solubility of the potassium content), sodium bitartrate TS produces a white crystalline precipitate, which is soluble in 6 *N* ammonium hydroxide and in solutions of alkali hydroxides and carbonates. The formation of the precipitate, which is usually slow, is accelerated by stirring or rubbing the inside of the test tube with a glass rod. The addition of a small amount of glacial acetic acid or alcohol also promotes the precipitation.

Salicylate—In moderately dilute solutions of salicylates, ferric chloride TS produces a violet color. The addition of acids to moderately concentrated solutions of salicylates produces a white, crystalline precipitate of salicylic acid, which melts between 158° and 161°.

Silver—Solutions of silver salts yield with hydrochloric acid a white, curdy precipitate, which is insoluble in nitric acid, but is readily soluble in 6 *N* ammonium hydroxide. A solution of a silver salt to which 6 *N* ammonium hydroxide and a small quantity of formaldehyde TS are added deposits, upon warming, a mirror of metallic silver upon the sides of the container.

Sodium—Solutions of sodium compounds after conversion to chloride or nitrate yield, with five times their volume of cobalti-uranyl acetate TS, a golden yellow precipitate, which forms after standing for several minutes. Sodium compounds impart an intense yellow color to a nonluminous flame.

Sulfate—Solutions of sulfates yield with barium chloride TS a white precipitate, which is insoluble in hydrochloric acid and in nitric acid. With lead acetate TS, sulfates yield a white precipitate, which is soluble in ammonium acetate solution. Hydrochloric acid produces no precipitate when added to solutions of sulfates (*distinction from thiosulfates*).

Sulfite—When treated with 3 *N* hydrochloric acid, sulfites and bisulfites yield sulfur dioxide, recognizable by its characteristic, pungent odor. This gas blackens filter paper moistened with mercurous nitrate TS.

Tartrate—Upon the addition of a few mg of a tartrate to a mixture of 15 ml of pyridine and 5 ml of acetic anhydride, an emerald-green color is produced.

Thiocyanate—Solutions of thiocyanates yield with ferric chloride a red color, which is not destroyed by moderately concentrated mineral acids.

Thiosulfate—Solutions of thiosulfates yield with hydrochloric acid a white precipitate which soon turns yellow, and sulfur dioxide, recognizable by its odor, is liberated. The addition of ferric chloride to solutions of thiosulfates produces a dark violet color which quickly disappears.

Zinc—In the presence of sodium acetate, solutions of zinc salts yield a white precipitate with hydrogen sulfide. This precipitate is insoluble in acetic acid, but is dissolved by 3 *N* hydrochloric acid. Ammonium sulfide TS produces a similar precipitate in neutral and alkaline solutions. Zinc salts in solution yield with potassium ferrocyanide TS a white precipitate, which is insoluble in 3 *N* hydrochloric acid.

⟨201⟩ THIN-LAYER CHROMATOGRAPHIC IDENTIFICATION TEST

The following procedure is applicable for confirming the identity of many Pharmacopeial drug substances as such and in their respective dosage forms.

Prepare a test solution as directed in the individual monograph. On a line parallel to and about 2 cm from the edge of a suitable thin-layer chromatographic plate, coated with a 0.25-mm layer of chromatographic silica gel with a suitable fluorescing substance (see ⟨621⟩), spot 10 µl of this solution and 10 µl of a Standard solution prepared from the USP Reference Standard for the drug substance being identified, in the same solvent and at the same concentration as the test solution, unless otherwise directed in the individual monograph. Allow the spots to dry, and develop the chromatogram in a solvent system consisting of 180 parts of chloroform, 15 parts of methanol, and 1 part of water, unless otherwise directed in the individual monograph, until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the developing chamber, mark the solvent front, and allow the solvent to evaporate. Unless otherwise directed in the individual monograph, locate the spots on the plate by examination under short-wavelength ultraviolet light. The R_f value of the main spot obtained from the test solution corresponds to that obtained from the Standard solution.

LIMIT TESTS

⟨211⟩ ARSENIC

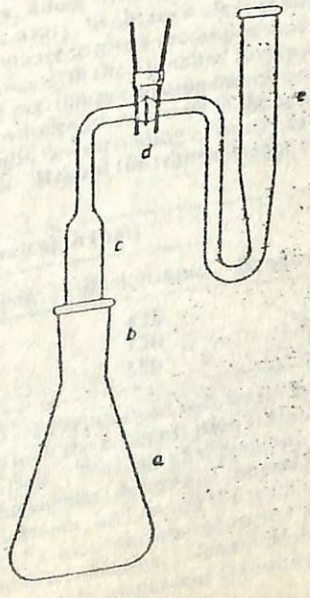
This photometric procedure, based upon the reaction between silver diethyldithiocarbamate and arsine, is provided to demonstrate that the content of arsenic does not exceed the limit given in the individual monograph.

Apparatus—The apparatus (see illustration)* consists of an arsine generator (*a*) fitted with a scrubber unit (*c*) and an absorber tube (*e*) with standard-taper or ground glass ball-and-socket joints (*b* and *d*) between the units. However, any other suitable apparatus, embodying the principle of the assembly described and illustrated, may be used.

Standard Preparation—Dissolve 132.0 mg of arsenic trioxide, previously dried at 105° for 1 hour and accurately weighed, in 5 ml of sodium hydroxide solution (1 in 5) in a 1000-ml volumetric flask. Neutralize the solution with 2 *N* sulfuric acid, add 10 ml more of 2 *N* sulfuric acid, then add recently boiled and cooled water to volume, and mix. Transfer 10.0 ml of this solution to a 1000-ml volumetric flask, add 10 ml of 2 *N* sulfuric acid, then add recently boiled and cooled water to volume, and mix. Each ml of *Standard Preparation* contains the equivalent of 1 µg of arsenic (As). Keep this solution in an all-glass container, and use within 3 days.

Test Preparation—[*Caution*—*Some substances may react with*

* A suitable apparatus is obtainable from Fisher Scientific Co., 711 Forbes Ave., Pittsburgh, Pa. 15219.



Arsenic Test Apparatus

explosive violence when digested with hydrogen peroxide. Exercise safety precautions at all times.]

[NOTE—If halogen-containing compounds are present, use a lower temperature while heating the test specimen with sulfuric acid, and boiling the mixture, and add the hydrogen peroxide with caution, before charring begins, to prevent loss of trivalent arsenic.]

Prepare the *Test Preparation* of an inorganic compound as directed in the individual monograph.

Prepare the *Test Preparation* of an organic compound in the generator flask (*a*), unless otherwise directed in the individual monograph, according to the following general procedure.

Unless otherwise directed in the individual monograph, transfer to the generator flask the quantity, in g, of the test substance calculated by the formula $3.0/L$, in which L is the arsenic limit, in ppm. Add 5 ml of sulfuric acid and a few glass beads, and digest on a hot plate or other suitable heating unit in a fume hood until charring begins. (Additional sulfuric acid may be necessary to wet some specimens completely, but the total volume added should not exceed 10 ml.) After the test substance has been initially decomposed by the acid, cautiously add, dropwise, 30 percent hydrogen peroxide, allowing the reaction to subside and again heating between drops. Add the first few drops very slowly with sufficient mixing, in order to prevent a rapid reaction. Discontinue heating if foaming becomes excessive. When the reaction has abated, heat cautiously, rotating the flask occasionally to prevent the specimen from caking on glass exposed to the heating unit. *Maintain oxidizing conditions at all times during the digestion by adding small quantities of the hydrogen peroxide solution whenever the mixture turns brown or darkens.* Continue the digestion until the organic matter is destroyed, fumes of sulfur trioxide are copiously evolved, and the solution becomes colorless or retains only a light straw color. Cool, add cautiously 10 ml of water, mix, and again evaporate to strong fuming, repeating this procedure, if necessary, to remove any trace of hydrogen peroxide. Cool, add cautiously 10 ml of water, wash the sides of the flask with a few ml of water, and dilute with water to 35 ml.

Procedure—If the *Test Preparation* was not prepared in the generator flask (*a*), transfer to the flask a volume of the solution prepared as directed in the individual monograph, and add water to make 35 ml. Add 20 ml of dilute sulfuric acid (1 in 5), 2 ml of potassium iodide TS, and 0.5 ml of stronger acid stannous chloride TS, and mix. Allow to stand at room temperature for 30 minutes. Pack the scrubber tube (*c*) with two pledgets of cotton that have been soaked in saturated lead acetate solution, freed from excess solution by expression, and dried in vacuum at room temperature, leaving a small space between the two pledgets. Lubricate the joints (if necessary) with a suitable stopcock grease (designed for use with organic solvents), and connect the scrubber unit to the absorber tube (*b* and *d*). Transfer 3.0 ml of silver diethyldithiocarbamate TS to the absorber tube. Alternatively, a larger accurately measured volume of the silver diethyldithiocarbamate TS may be employed, provided that the same volume is used for the control test and that the apparatus will accommodate the larger volume. Add 3.0 g of granular zinc (No. 20 mesh) to the mixture in the flask, immediately connect the assembled scrubber unit, place the generator flask (*a*) in a water bath maintained at a temperature of 25 ± 3°, and allow the evolution of hydrogen and the color development to proceed for 45 minutes, swirling the flask gently at 10-minute intervals. (If necessary, to obtain a more uniform rate of gas evolution, 1 ml of isopropyl alcohol may be added to the generator.) Disconnect the absorber tube from the generator and scrubber units, and transfer the absorbance solution to a 1-cm absorption cell. Determine the absorbance at the wavelength of maximum absorbance between 535 and 540 nm, with a suitable spectrophotometer or colorimeter, using silver diethyldithiocarbamate TS as the blank. The absorbance due to any red color from the test solution does not exceed that produced by 3.0 ml of *Standard Preparation* (3.0 µg of As) similarly treated with the same quantities of the same reagents and in the same manner.

If the *Test Preparation* was prepared as directed in the general procedure for organic compounds, mix the portion of *Standard Preparation* with 2 ml of sulfuric acid and the total amount of 30 percent hydrogen peroxide used in the oxidation of the test specimen, heat the mixture to strong fuming, cool, add cautiously 10 ml of water, again evaporate to strong fuming, and cool. Dilute with water to 35 ml, and proceed as directed in the first paragraph under *Procedure*, beginning with "Add 20 ml of dilute sulfuric acid (1 in 5)."

Interfering Chemicals—Metals or salts of metals such as chromium, cobalt, copper, mercury, molybdenum, nickel, palladium, and silver may interfere with the evolution of arsine. *Antimony*, which forms stibine, produces a positive interference in the color development with silver diethyldithiocarbamate TS; when the presence of antimony is suspected, the red colors produced in the two silver diethyldithiocarbamate solutions may be compared at the wavelength of maximum absorbance between 535 nm and 540 nm, with a suitable colorimeter, since at this wavelength the interference due to stibine is negligible.

⟨216⟩ CALCIUM, POTASSIUM, AND SODIUM

The flame photometer characteristically is equipped with a photomultiplier phototube detector for determination of calcium or sodium, a red-sensitive phototube detector for the determination of potassium, a monochromator, an adjustable exit slit, sensitivity controls, and an oxyacetylene burner. An oxyhydrogen burner is necessary for the determination of potassium in the presence of large amounts of calcium.

Standard Calcium Ion Solution—Transfer 249.7 mg of calcium carbonate to a 100-ml volumetric flask, dissolve in a mixture of 20 ml of water and 5 ml of 3 *N* hydrochloric acid, dilute with water to volume, and mix. Each ml contains 1.00 mg of calcium ion (Ca).

Standard Potassium Ion Solution—Transfer 190.7 mg of potassium chloride to a 100-ml volumetric flask, dissolve in water, dilute with water to volume, and mix. Each ml contains 1.00 mg of potassium ion (K).

Standard Sodium Ion Solution—Transfer 254.2 mg of sodium chloride to a 100-ml volumetric flask, dissolve in water, dilute with water to volume, and mix. Each ml contains 1.00 mg of sodium ion (Na).

Standard Preparation—Transfer a 50-ml aliquot of the *Test Preparation* to a 100-ml volumetric flask, add the volume(s) of *Standard Ion Solution*(*s*) specified in the individual monograph, dilute with water to volume, and mix. Quantitatively dilute aliquots of this solution with water as necessary to bring the concentration of the ion to be determined into the proper range for the flame photometer used.

Test Preparation—Unless otherwise directed in the individual monograph, transfer 2.000 g of test specimen to a 100-ml volumetric flask, chill in an ice bath, add 5 ml of nitric acid, swirl to dissolve, and allow to warm to room temperature. Heat gently, if necessary, to obtain a clear or just slightly turbid mixture. Cool to room temperature, if necessary, dilute with water to volume, and mix. Filter or centrifuge if necessary, to obtain a clear solution.

Adjust the flame photometer to give a reading as near as possible to 100 percent transmittance with the *Standard Preparation* at the wavelength setting giving maximum emission corresponding to the designated characteristic wavelength as shown in the accompanying table. Use an exit slit width corresponding as nearly as possible to the designated bandwidth. Record the transmittance reading, labeling it as *S*.

Ion	Wavelength (nm)		Bandwidth (nm)
	Characteristic	Background	
Calcium	422.7	430	0.8
Potassium	766.5	750	12
Sodium	589	580	0.8

Dilute aliquots of the *Test Preparation* with water as necessary to prepare a solution in which the concentration is similar to that in the *Standard Preparation*. Without changing any of the adjustments of the flame photometer, determine the emission of the solution as percent transmittance, and record the reading, labeling it as *T*. Readjust only the monochromator to the designated wavelength for background determination. Determine the emission of the solution at this wavelength as percent transmittance, and record the reading, labeling it as *B*.

The requirements of the test are met if the value of *T* minus *B* is less than or equal to the value of *S* minus *T*.

(221) CHLORIDE AND SULFATE

The following limit tests are provided as general procedures for chloride limits for chloride and sulfate are specified in the individual monographs.

Perform the tests and the controls in glass cylinders of the same color and matched as closely as practicable in other respects (see *Color and Comparison* (851)). Use the same quantities of the same reagents for both the solution under test and the control solution containing the specified volume of chloride or sulfate. If, after precipitation, the solution is not perfectly clear, filter it through a filter paper that gives negative tests for chloride and sulfate. Add the precipitant, silver nitrate TS or barium chloride TS as required, to both the test solution and the control solution in immediate succession.

Where the individual monograph calls for applying the test to a specific volume of a solution of the substance, and the limit for chloride or sulfate corresponds to 0.2 ml or less of 0.020 *N* hydrochloric acid VS or sulfuric acid VS, respectively, apply the test to the solution without further dilution. In such cases maintain the volume relationships for the control solution as specified for the solution under test. In applying the test to the salts of heavy metals, which normally show an acid reaction, omit the acidification that would neutralize the solution. Dissolve bismuth salts in a few drops of water and 2 ml of nitric acid before treating with the precipitant.

Chloride—Dissolve the specified quantity of the substance under test in 30 to 40 ml of water, or, where the substance is already in solution, add water to make a total volume of 30 to 40 ml, and, if necessary, neutralize the solution to litmus with nitric acid. Add 1.25 ml of nitric acid and of silver nitrate TS, and sufficient water to make 50 ml. Mix, allow to stand for 5 minutes protected from direct sunlight, and compare the turbidity, if any, with that produced in a solution containing the volume of 0.020 *N* hydrochloric acid specified in the monograph.

Sulfate—Dissolve the specified quantity of the substance under test in 30 to 40 ml of water, or, where the substance is already in solution, add water to make a total volume of 30 to 40 ml, and, if necessary, neutralize the solution to litmus with hydrochloric acid. Add 2 ml of 3 *N* hydrochloric acid, 3 ml of barium chloride TS, and sufficient water to make 50 ml. Mix, allow to stand for 10 minutes, and compare the turbidity, if any, with that produced in a solution containing the volume of 0.020 *N* sulfuric acid VS specified in the monograph.

(231) HEAVY METALS

This test is provided to demonstrate that the content of metallic impurities that are colored by sulfide ion, under the specified test conditions, does not exceed the *Heavy metals* limit specified in the individual monograph in terms of the percentage (by weight) of lead in the test substance, as determined by concomitant visual comparison (see *Visual Comparison* under *Procedure* (851)) with a control prepared from a *Standard Lead Solution*.

Choose the amount of heavy metals by *Method I*, unless otherwise specified in the individual monograph. *Method I* is used for substances that yield clear, colorless preparations under the specified test conditions. *Method II* is used for substances that do not yield clear, colorless preparations under the test conditions required for *Method I*, or for substances that, by virtue of their chemical nature, interfere with the precipitation of metals by sulfide ion. *Method III*, a wet-digestion procedure, is used only in those cases where neither *Method I* nor *Method II* can be utilized.

Special Reagents

Lead Nitrate Stock Solution—Dissolve 159.8 mg of lead nitrate in a 100-ml portion of water to which has been added 1 ml of nitric acid, then dilute with water to 1000 ml. Prepare and store this solution in containers free from soluble lead salts.

Standard Lead Solution—On the day of use, dilute 10.0 ml of *Lead Nitrate Stock Solution* with water to 100.0 ml. Each ml of *Standard Lead Solution* contains the equivalent of 10 µg of lead. Use this solution prepared on the basis of 100 µl of *Standard Lead Solution* per 2 ml of the solution prepared as directed in the individual monograph, unless otherwise specified in the individual monograph. Use the same quantities of the same reagents for both the solution under test and the control solution containing the specified volume of lead. If, after precipitation, the solution is not perfectly clear, filter it through a filter paper that gives negative tests for lead. Add the precipitant, hydrogen sulfide TS, to both the test solution and the control solution in immediate succession.

Where the individual monograph calls for applying the test to a specific volume of a solution of the substance, and the limit for lead corresponds to 0.2 ml or less of 0.020 *N* lead nitrate VS, apply the test to the solution without further dilution. In such cases maintain the volume relationships for the control solution as specified for the solution under test. In applying the test to the salts of heavy metals, which normally show an acid reaction, omit the acidification that would neutralize the solution. Dissolve bismuth salts in a few drops of water and 2 ml of nitric acid before treating with the precipitant.

Method I

Standard Preparation—Into a 50-ml color-comparison tube pipet 2 ml of *Standard Lead Solution* (20 µg of Pb), and dilute with water to 25 ml. Adjust with 1 *N* acetic acid or 6 *N* ammonium hydroxide to a pH between 3.0 and 4.0, using short-range pH indicator paper as external indicator, dilute with water to 40 ml, and mix.

Test Preparation—Into a 50-ml color-comparison tube place 25 ml of the solution prepared for the test as directed in the individual monograph, or, using the designated volume of acid where specified in the individual monograph, dissolve and dilute with water to 25 ml the quantity, in g, of the substance to be tested, as calculated by the formula $2.0/(1000L)$, in which L is the *Heavy metals* limit, in percentage. Adjust with 1 *N* acetic acid or 6 *N* ammonium hydroxide to a pH between 3.0 and 4.0, using short-range pH indicator paper as external indicator, dilute with water to 40 ml, and mix.

Monitor Preparation—Into a third 50-ml color-comparison tube place 25 ml of a solution prepared as directed for *Test Preparation*, and add 2.0 ml of *Standard Lead Solution*. Adjust with 1 *N* acetic acid or 6 *N* ammonium hydroxide to a pH between 3.0 and 4.0, using short-range pH indicator paper as external indicator, dilute with water to 40 ml, and mix.

Procedure—To each of the three tubes containing the *Standard Preparation*, the *Test Preparation*, and the *Monitor Preparation*, respectively, add 10 ml of freshly prepared hydrogen sulfide TS, mix, allow to stand for 5 minutes, and view downward over a white surface. The color of the solution from the *Test Preparation* is not darker than that of the solution from the *Standard Preparation*, and the intensity of the color of the *Monitor Preparation* is equal to or greater than that of the *Standard Preparation*. The color of the *Monitor Preparation* is lighter than that of the *Standard Preparation*, use *Method II* instead of *Method I* for the substance being tested.]

Method II

Standard Preparation—Prepare as directed under *Method I*.

Test Preparation—Use a quantity, in g, of the substance to be tested as calculated by the formula $2.0/(1000L)$, in which L is the *Heavy metals* limit, in percentage. Transfer the weighed quantity of the substance to a suitable crucible, add sufficient sulfuric acid to wet the substance, and carefully ignite at a low temperature until thoroughly charred. (The crucible may be loosely covered with a suitable lid during the charring.) Add to the carbonized mass 2 ml of nitric acid and 5 drops of sulfuric acid, and heat cautiously until white fumes no longer are evolved. Ignite, preferably in a muffle furnace, at 500° to 600°, until the carbon is completely burned off. Cool, add 4 ml of 6 *N* hydrochloric acid, cover, digest on a steam bath for 15 minutes, uncover, and slowly evaporate on a steam bath to dryness. Moisten the residue with 1 drop of hydrochloric acid, add 10 ml of hot water, and digest for 2 minutes. Add 6 *N* ammonium hydroxide dropwise, until the solution is just alkaline to litmus paper, dilute with water to 25 ml, and adjust with 1 *N* acetic acid to a pH between 3.0 and 4.0, using short-range pH indicator paper as external indicator. Filter if necessary, rinse the crucible and the filter with 10 ml of water, combine the filtrate and rinsing in a 50-ml color-comparison tube, dilute with water to about 40 ml, and mix.

Procedure—To each of the tubes containing the *Standard Preparation* and the *Test Preparation*, respectively, add 10 ml of freshly prepared hydrogen sulfide TS, mix, dilute with water to 50 ml, allow to stand for 5 minutes, and view downward over a white surface: the color of the solution from the *Test Preparation* is not darker than that of the solution from the *Standard Preparation*.

Method III

Standard Preparation—Transfer a mixture of 8 ml of sulfuric acid and 10 ml of nitric acid to a clean, dry, 100-ml Kjeldahl flask, and add a further volume of nitric acid equal to the incremental volume of nitric acid added to the *Test Preparation*. Heat the solution to the production of dense, white fumes, cool, cautiously add 10 ml of water and, if hydrogen peroxide was used in treating the *Test Preparation*, add a volume of 30 percent hydrogen peroxide equal to that used for the substance being tested, and boil gently to

standard preparations are made available by the Bureau of Biologics (Section 610.20), such preparations are specified for comparison in potency or virulence testing. The U. S. Opacity Standard is used in estimating the bacterial concentration of all bacterial vaccines. (See also *Units of Potency*, in the *General Notices*.)

The Pharmacopeial monographs conform to the Food and Drug Regulations in covering those aspects of identity, quality, purity, potency, and packaging and storage that are of particular interest to pharmacists and physicians responsible for the purchase, storage and use of biologics. Revisions of the federal requirements affecting the USP monographs will be made the subjects of USP Supplements as promptly as practicable.

Vehicles and Added Substances—Vehicles and added substances suitable for biologics are those named in the Food and Drug Regulations.

Containers for Injections—Containers for biologics intended to be administered by injection meet the requirements for *Containers for Injections* under *Injections* ⟨1⟩.

Volume in Container—The volumes in containers of biologics intended to be administered by injection meet the requirements for *Volume in Container* under *Injections* ⟨1⟩.

Labeling—Biologics intended to be administered by injection comply with the requirements for *Labeling* under *Injections* ⟨1⟩. In addition, the label on the final container for each biologic states: the title or proper name (the name under which the product is licensed under the Public Health Service Act); the name, address, and license number of the manufacturer; the lot number; the expiration date; and the recommended individual dose for multiple-dose containers. The package label includes all of the above, with the addition of: the preservative used and its amount; the number of containers, if more than one; the amount of product in the container; the recommended storage temperature; a statement, if necessary, that freezing is to be avoided; and such other information as the Food and Drug regulations may require.

Packaging and Storage—The labeling gives the recommended storage temperature (see *General Notices*). Precautions should be taken where products labeled to be stored at a temperature between 2° and 8° are stored in a refrigerator, in order to assure that they will not be frozen. Diluents packaged with biologics should not be frozen. Some products (as defined in Section 600.15) are to be maintained during shipment at specified temperatures.

⟨1051⟩ CLEANING GLASS APPARATUS

Success in conducting many Pharmacopeial assays depends upon the utmost cleanliness of the apparatus used. To be mentioned especially in this connection are the assays of heparin sodium and of vitamin B_{12} activity, and the pyrogen test.

For cleaning glassware, one of the most effective agents is hot nitric acid. An effective method of removing organic matter from glassware without heating is by treatment with a chromic acid cleansing mixture as described herein. Crystalline chromic acid tends to separate from the mixture on standing, and may be removed by decantation. Glass tends to adsorb the chromic acid, which makes long rinsing imperative. Alkaline cleansing agents, such as trisodium phosphate and the synthetic detergents, are highly useful but also require following rinsing. Special care is required for cleaning containers used for optical measurements, and the use of both chromic acid and highly alkaline solutions should be avoided.

Chromic Acid Cleansing Mixture may be prepared as follows:

Chromic Acid Cleansing Mixture

Sodium Dichromate	200 g
Water	100 ml
Sulfuric Acid	1500 ml

Dissolve the sodium dichromate in the water, and slowly and cautiously add the sulfuric acid, with stirring. *Wear safety goggles. Prepare this mixture in a hard, heat-resistant glass, 2000-ml beaker, since the heat produced may cause soft-glass containers to break. Chromic Acid Cleansing Mixture is extremely corrosive and hygroscopic, and should be stored in glass-stoppered bottles in a safe place. When the mixture has acquired a green color, it should not be returned to the storage bottle, but should be discarded under continuously flowing water.*

⟨1061⟩ COLOR—INSTRUMENTAL MEASUREMENT

The observed color (see *Color and Achromicity* ⟨631⟩) of an object depends on the spectral energy of the illumination, the absorbing characteristics of the object, and the visual sensitivity of the observer over the visible range. Similarly, it is essential that any instrumental method that is widely applicable take these same factors into account.

An instrumental method provides an objective, accurate, and precise way of measuring color and color differences. It is based on the principle that any color can be considered as a specific mixture of three suitably chosen lights or stimuli. Conversely, a statement of the amount of each light needed to match a color uniquely defines that color. Although no single set of three real lights can be used to match all colors, three arbitrary stimuli have been defined, with which it is possible to specify all real colors. The amounts of each stimulus needed for the match are called the *tristimulus values* (X, Y, Z) of the color.

The nature of the relationship between the tristimulus values and the observed color has been determined by color-matching experiments with human subjects having normal color vision. This relationship is given by the distribution coefficients $\bar{x}_\lambda \bar{y}_\lambda \bar{z}_\lambda$ (see accompanying figure) in the equations

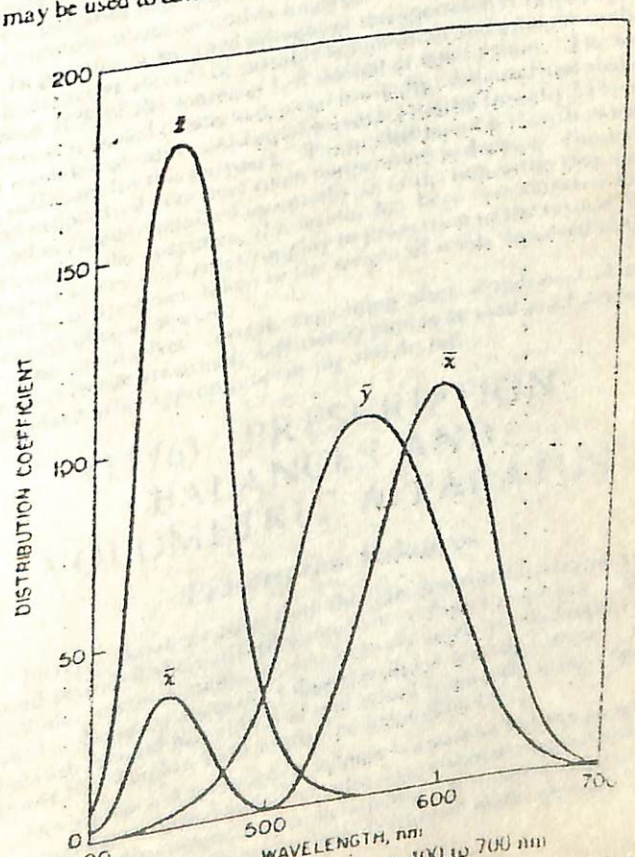
$$X = \int_0^\infty f_\lambda \bar{x}_\lambda P_\lambda d\lambda / Y'',$$

$$Y = \int_0^\infty f_\lambda \bar{y}_\lambda P_\lambda d\lambda / Y'',$$

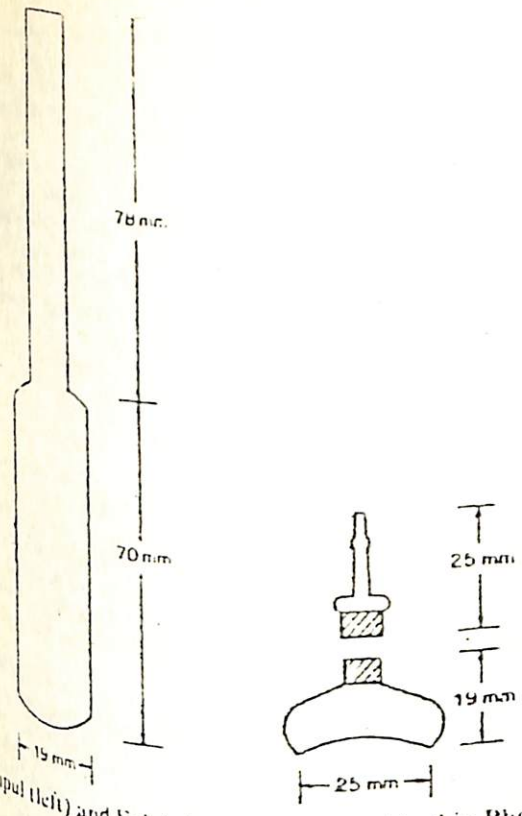
$$Z = \int_0^\infty f_\lambda \bar{z}_\lambda P_\lambda d\lambda / Y'',$$

in which $Y'' = \int_0^\infty \bar{y}_\lambda P_\lambda d\lambda$, P_λ is the spectral power of the illuminant, and f_λ is either the spectral reflectance (ρ_λ) or spectral transmittance (τ_λ) of the material.

Once the tristimulus values of a color have been determined, they may be used to calculate the coordinates of the color in an idealized



Distribution Coefficients from 400 to 700 nm



Ampul (left) and Solubility Flask (right) Used in Phase-solubility Analysis

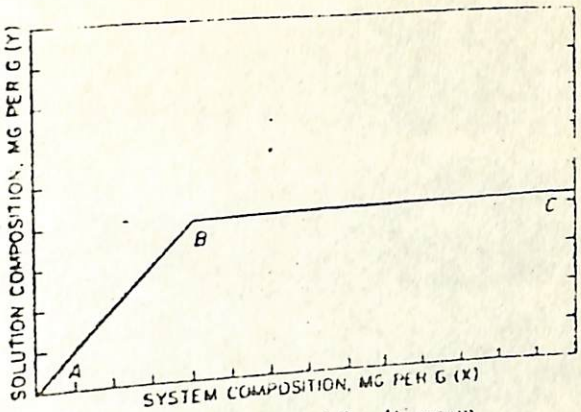
ampul contains slightly less material than will go into solution in ml of the selected solvent, the second ampul contains slightly more material, and each subsequent ampul contains increasingly more material than meets the indicated solubility. Transfer 5.0 ml of the solvent to each of the ampuls, cool in a dry ice–acetone mixture, and seal, using a doublet-jet air–gas burner and taking care to save all glass. Allow the ampuls and their contents to come to room temperature, and weigh the individual sealed ampuls with the corresponding glass fragments. Calculate the system composition, in mg per g, for each ampul by the formula $1000(W_2 - W_1)/(W_3 - W_1)$, in which W_2 is the weight of the ampul plus test substance, W_1 is the weight of the empty ampul, and W_3 is the weight of ampul plus test substance, solvent, and separated glass.

Equilibration—The time required for equilibration varies with the substance, the method of mixing (rotation or vibration), and the temperature. Normally, equilibrium is obtained more rapidly by the vibration method (1 to 7 days) than by the rotational method (7 to 14 days). In order to determine whether equilibration has been effected, 1 ampul, i.e., the next to the last in the series, may be warmed to 40° to produce a super-saturated solution. Equilibration is assured if the solubility obtained on the super-saturated solution falls in line with the test specimens that approach equilibrium from an undersaturated solution.

Solution Composition—After equilibration, place the ampuls vertically in a rack in the constant-temperature bath, with the necks of the ampuls above the water level, and allow the contents to settle. Open the ampuls, and remove a portion greater than 2 ml from each by means of a pipet equipped with a small pledget of cotton membrane or other suitable filter. Transfer a 2.0-ml aliquot of clear solution from each ampul to a marked, tared solubility flask, and weigh each flask plus its solution to obtain the weight of the solution. Cool the flasks in a dry ice–acetone bath, and then evaporate the solvent in vacuum. Gradually increase the temperature to a temperature consistent with the stability of the compound, and dry the residue to constant weight. Calculate the solution composition, in mg per g, by the formula $1000(F_3 - F_1)/(F_2 - F_3)$, in which F_3 is the weight of the flask plus residue, F_1 is the weight of the solubility flask, and F_2 is the weight of the flask plus solution.

Calculation

For each portion of the test substance taken, plot the solution composition as the ordinate and the system composition as the abscissa. As shown in the accompanying diagram, the points for those solutions, frequently only one, that represent a true solution fall



Typical Phase-solubility Diagram

on a straight line (AB) with a slope of 1, passing through the origin; the points corresponding to saturated solutions fall on another straight line (BC), the slope, S, of which represents the weight fraction of impurity or impurities present in the test substance. Failure of points to fall on a straight line indicates that equilibrium has not been achieved. A curve indicates the material under test may be a solid solution. Calculate the percentage purity of the test substance by the formula $100 - 100S$. The slope, S, may be calculated graphically or by least-squares treatment for best fit of the experimental values to a straight line.

The solubility of the main component is obtained by extending the solubility line (BC) through the y-axis. The point of interception on the y-axis is the extrapolated solubility, in mg per g, and is a constant for a given compound.

Purification Technique

Since the solvent phase in all combinations of solvent and solute that are used to construct segment BC of a phase-solubility diagram contains essentially all of the impurities originally present in the substance under analysis, while the solid phase is essentially free from impurities, phase-solubility analysis can be used to prepare pure reference specimens of desired compounds as well as concentrates of impurities from substances otherwise considered pure. A simple modification of this technique can be used to accomplish these purposes with considerably less effort than is usually required for rigorous phase-solubility analysis.

In practice, a weighed amount of test specimen is suspended in a nonreactive solvent of suitable composition and amount so that about 10% of the material is dissolved at equilibrium. The suspension is sealed (a screw-cap vial is usually adequate) and shaken at room temperature until equilibrium is attained (usually 24 hours is sufficient for this purpose). The mother liquor is then drawn off and evaporated at or near room temperature to dryness. Since the mother liquor contained essentially all of the impurities that were present in the specimen, the residue has been concentrated with respect to the impurities roughly in proportion to the ratio of the weight of specimen taken to the weight of solids dissolved in the volume of solvent used.

The undissolved crystals remaining after withdrawal of the mother liquor are usually sufficiently pure to be used as a reference standard after appropriate rinsing and drying.

⟨1176⟩ PRESCRIPTION BALANCES AND VOLUMETRIC APPARATUS

Prescription Balances

NOTE—Balances other than the type described herein may be used provided these afford equivalent or better accuracy. This includes micro-, semimicro-, or electronic simple-pan-balances (see ⟨41⟩). Some balances offer digital or direct-reading features. All balances should be calibrated and tested frequently using appropriate test weights, both singly and in combination.

Description—A prescription balance is a scale or balance adapted to weighing medicinal and other substances required in prescriptions or in other pharmaceutical compounding. It is constructed so as to support its full capacity without developing undue stresses, and

weighbeam is not affected by repeated weighings of the capacity load. The removable pans or weighing vessels should be of equal weight. The balance should have leveling feet or screws. The balance may feature dial-in weights and also a precision spring and that instead of a weighbeam. A balance that has a graduated weighbeam must have a stop that holds the rider or poise at the "zero" reading. The reading edge of the rider is parallel to the graduations on the weighbeam. The distance from the face of the index plate to the indicator pointer or pointers should be not more than 1.6 mm (0.04 inch), the points should be sharp, and when there are two, their ends should be separated by not more than 1.0 mm (1/64 inch) when the scale is in balance. The indicating elements of the lever system should be protected against drafts, and the balance lid should permit free movement of the loaded weighing pans when the lid is closed. The balance must have a mechanical arresting device.

Definitions—

Capacity—Maximum weight, including the weight of tares, to be placed on one pan. The *N.B.S. Handbook 44*, 4th ed., states: "*In the absence of information to the contrary*, the nominal capacity of a Class *A* balance shall be assumed to be 15.5 g (½ apothecaries' ounce)." Most of the commercially available Class *A* balances have a capacity of 120 g (4 ounces) and bear a statement to that effect.

Weighbeam or Beam—A graduated bar equipped with a movable poise or rider. Metric graduations are in 0.01-g increments up to a maximum of 1.0 g; apothecaries' graduations are in ⅛-grain increments up to a maximum of 15⅜ grains. The bar may be graduated in both systems.

Tare Bar—An auxiliary ungraduated weighbeam bar with a movable poise. This can be used to correct for variations in weighing-glasses or papers.

Balance Indicator—A combination of elements, one or both of which will oscillate with respect to the other, to indicate the equilibrium state of the balance during weighing.

Rest Point—The point on the index plate at which the indicator or pointer stops when the oscillations of the balance cease; or the index plate position of the indicator or pointer calculated from recorded consecutive oscillations in both directions past the "zero" of the index plate scale. If the balance has a two-pointer indicating mechanism, the position or the oscillations of only one of the pointers need be recorded or used to determine the rest point.

Sensitivity Requirements (SR)—The maximum change in load that will cause a specified change, one subdivision on the index plate, in the position of rest of the indicating element or elements of the balance.

Class A Prescription Balance—A balance that meets the tests for this type of balance has a sensitivity requirement of 6 mg or less with no load and with a load of 10 g on each pan. The Class *A* balance should be used for all of the weighing operations required in prescription compounding.

In order to avoid errors of 5 percent or more that might be due to the limit of sensitivity of the Class *A* prescription balance, do not weigh less than 120 mg (2 grains) of any material. If a smaller weight of dry material is required, mix a larger known weight of the ingredient with a known weight of dry diluent, and weigh an aliquot portion of the mixture for use.

Testing the Prescription Balance—A Class *A* prescription balance meets the following four basic tests. Use a set of test weights, and keep the rider on the weighbeam at zero unless directed to change its position.

1. *Sensitivity Requirement*—Level the balance, determine the rest point, and place a 6-mg weight on one of the empty pans. Repeat the operation with a 10-g weight in the center of each pan. The rest point is shifted not less than one division on the index plate each time the 6-mg weight is added.

2. *Arm Ratio Test*—This test is designed to check the equality of length of both arms of the balance. Determine the rest point of the balance with no weight on the pans. Place in the center of each pan a 30-g test weight, and determine the rest point. If the second rest point is not the same as the first, place a 20-mg weight on the lighter side, the rest point should move back to the original place on the index plate scale or farther.

3. *Shift Tests*—These tests are designed to check the arm and lever components of the balance.

a. Determine the rest point of the indicator without any weights on the pans.

b. Place one of the 10-g weights in the center of the left pan, and place the other 10-g weight successively toward the right, left, front, and back of the right pan, noting the rest point in each case. If in any case the rest point differs from the rest point determined in Step *A*, add a 10-mg weight to the lighter side; this should cause the rest point to shift back to the rest point determined in Step 1 or farther.

c. Place a 10-g weight in the center of the right pan, and place a 10-g weight successively toward the right, left, front, and back of the left pan, noting the rest point in each case. If in any case the rest point is different from that obtained with no weights on the pans, this difference should be overcome by addition of the 10-mg weight to the lighter side.

D. Make a series of observations in which both weights are simultaneously shifted to off-center positions on their pans, both toward the outside, both toward the inside, one toward the outside and the other toward the inside, both toward the back, and so on until all combinations have been checked. If in any case the rest point differs from that obtained with no weights on the pan, the addition of the 10-mg weight to the lighter side should overcome this difference.

A balance that does not meet the requirements of these tests must be adjusted.

4. *Rider and Graduated Beam Tests*—Determine the rest point for the balance with no weight on the pans. Place on the left pan the 500-mg test weight, move the rider to the 500-mg point on the beam, and determine the rest point. If it is different from the zero rest point, add a 6-mg weight to the lighter side. This should bring the rest point back to its original position or farther. Repeat this test, using the 1-g test weight and moving the rider to the 1-g division on the beam. If the rest point is different, it should be brought back at least to the zero rest point position by addition of 6 mg to the lighter pan. If the balance does not meet this test, the weighbeam graduations or the rider must be corrected.

Metric or apothecaries' weights for use with a prescription balance should be kept in a special rigid and compartmentalized box and handled with plastic or plastic-tipped forceps to prevent scratching or soiling. For prescription use, analytical weights (Class P or better) are recommended. However, Class Q weights have tolerances well within the limits of accuracy of the prescription balance, and they retain their accuracy for a long time with proper care. Apothecaries' weights should have the same general (cylindrical) construction as metric weights. Coin-type (or disk-shaped) weights should not be used.

Test weights consisting of two 20-g or two 30-g, two 10-g, one 1-g, one 500-mg, one 20-mg, one 10-mg, and one 6-mg (or suitable combination totaling 6 mg) weights, adjusted to N.B.S. tolerances for analytical weights (Class P or better) should be used for testing the prescription balances. These weights should be kept in a tightly closed box and should be handled only with plastic or plastic-tipped forceps. The set of test weights should be used only for testing the balance or constantly used weights. If properly cared for, the set lasts indefinitely.

Volumetric Apparatus

Pharmaceutical devices for measuring volumes of liquids, including burets, pipets, and cylinders graduated either in metric or apothecary units meet the standard specifications for glass volumetric apparatus described in NTIS COM-73-10504 of the National Technical Information Service.[1] Conical graduates meet the standard specifications described in Handbook 44, 4th Edition of the National Bureau of Standards.[2] Graduated medicine droppers meet the specifications (see *Medicine Dropper* ⟨1101⟩). An acceptable ungraduated medicine dropper has a delivery tip 3 mm in external diameter and delivers 20 drops of water, weighing 1 g at a temperature of 15°. A tolerance of ± 10% of the delivered specification is reasonable.

Selection and Use of Graduates—

Capacity—The capacity of a graduate is the designated volume at the maximum graduation, that the graduate will contain, or deliver, as indicated, at the specified temperature.

Cylindrical and Conical Graduates—The error in a measured volume caused by a deviation of ±1 mm, in reading the lowest or

[1] NTIS COM-73-10504 is for sale by the National Technical Information Service, Springfield, Va. 22151.

[2] N.B.S. Handbook 44, 4th ed. (1971) is for sale by the Superintendent of Documents, U. S. Government Printing Office, Washington, D. C. 20402.

...ssociated problems with respect to sterility and ...ability, all extemporaneous parenteral preparations ...ed within 24 hours unless data are available to support ...ge.

...ing and Educating the Patient— As a final step in meeting ...ility for the stability of drugs dispensed, the pharmacist ...ld to inform the patient regarding the proper storage ...ons (example, in a cool, dry place—not in the bathroom), ...prescription and nonprescription products, and to suggest ...e estimate of the time after which the medication should ...ded. Where expiration dates are applied, the pharmacist ...phasize to the patient that the dates are applicable only ...per storage conditions are used. Patients should be en...d to clean out their drug storage cabinets periodically.

⟨1211⟩ STERILIZATION[1]

...method of attaining sterility in an article is determined by ...re of the product and the process of manufacture. Five ...od sterilization are described in this informational chapter. ...ose of the appropriate process requires a high level of ...ge and experience concerning the sterilization process and ...ntrol and its effects on product quality.

...sterilization process requires not only vigilant supervision ...ipment, instruments, and procedures for operation, mainte...and calibration by personnel well trained in devising and ...g methods for attaining sterility, but also adequate proof of ...ccess of the procedures used.

...establishment, validation, and monitoring of the sterilization ...ure requires the incorporation of appropriate physical, ...al and microbiological measurements to confirm that the ...ess carried out within prescribed guidelines. Instrumen...ed techniques employed to measure and record these pa...should qualify as equivalent to the most modern available ...of accuracy and reproducibility. Where appropriate, ...ng should include the employment of properly designed and ...ated biological indicators.

...addition to demonstrating the continuing effectiveness of the ...ation procedure, the article also should be periodically ...ed microbiologically prior to sterilization to assure that the ...cal bioburden established on validation has not significantly ...ed. The microorganisms recovered during testing of articles and ...environment should be characterized, and a record should be ...ained.

Methods of Sterilization

STEAM STERILIZATION

...process is ordinarily carried out in an autoclave and employs ...ted steam under pressure. Unless otherwise indicated, steam ...sterilization, where mentioned in this Pharmacopeia, denotes ...ment in an autoclave employing saturated steam under pressure ...ffect to the article a lethality factor (F_o) of 8. The use of steam ...sterilization under conditions delivering a lethality factor[2] less ...ne requires experimental data establishing the adequacy of the ...ve conditions. In this Pharmacopeia, where sterilization ...autoclave is specified for media and reagents, it refers to such ...sterilization at a minimum of 121° for not less than 15 min...

...The temperature at which autoclaves are operated is usually 121° ...trolled by a temperature-sensing device located in the steam ...free line of the autoclave. Inasmuch as the process depends ...the presence of moisture as well as elevated temperature, ad...measures must be taken to ensure that all air has been re...from the chamber prior to the initiation of the sterilizing ...cycle. The time of product exposure to temperature (heat-up, holding, and cooling) varies with the nature of the product and the size of the containers being treated. A solution packaged in thin-walled, 50-ml ampuls may reach a temperature of 121° from 6 to 8 minutes after this temperature is registered at the steam discharge line, whereas 20 minutes or more may be required in the case of a solution packaged in thick-walled, 1000-ml glass bottles. [NOTE— Where solutions are sterilized in rigid containers, high internal pressure build-up during the post-sterilization cooling phase may be hazardous to the safety of the sterilizer operators as a result of bursting containers. The containers may have vented closures or the system may have specially designed cooling processes to allow safe removal of the sterilized, hermetically sealed (non-vented) containers from the chamber.]

It is important to check the heat distribution, particularly in new or remodeled autoclaves or following changes in loading conditions, by placing suitable devices to register the temperatures attained at different horizontal and vertical planes in the sterilizing chamber. For this purpose, recording thermocouples sealed into representative containers of the preparation to be sterilized are suggested. During routine processing, these instruments give a much better indication of actual conditions in the autoclave than can be obtained from a record of the temperature at the steam discharge line alone. Other types of temperature-sensing indicators may be employed. These devices should be capable of indicating not only the attainment of an effective sterilization temperature, but also the duration of that temperature and, if necessary, of the temperatures of the heat-up and cooling phases of the sterilization cycle. The use of a recording thermometer in the steam discharge line is desirable for operational purposes and also to provide a permanent record of each sterilization cycle. Recording thermocouples or thermometers should be periodically calibrated with certified mercury glass thermometers.

Some types of steam sterilizers, especially those of the pre-vacuum type, tend to overheat and reduce the moisture content of the chamber to the extent that incomplete sterilization results. Other hazards may arise with small loads because of residual air in the chamber space or leakage of air into the evacuated chamber. Such pockets of air in small recessed areas are resistant to steam permeation and heating. These and other cycle deficiencies can be assessed by monitoring with suitable instruments. Biological indicators (see *Biological Indicators*) may be useful for demonstrating the adequacy of the sterilization process.

DRY-HEAT STERILIZATION

This process is usually carried out in a sterilizing oven designed specifically for the purpose. This is heated, normally, by gas or electricity and, except in the case of small models, is provided with a fan or blower to circulate the heated air to assure adequate heat distribution throughout the chamber. Temperature-recording devices should be employed.

Where dry heat is used, higher temperatures and longer periods of exposure are required than for steam sterilization. Specific time and temperature schedules must be determined for each type of material treated, and when the nature of the material permits, a generous safety factor should be included in the exposure time in order to compensate for differences in the heat-up period and for other variables that may affect the cycle. The size and nature of the units of material being treated and their distribution within the heating chamber are determining factors in the sterilization cycle. In general, individual units should be as small as possible and the sterilizer should be loaded in such manner as to permit free circulation of heated air throughout the chamber. Dry-heat sterilization is generally carried out at 160° to 170° for a period of not less than 2 hours. Higher temperatures and correspondingly shorter times may be employed for heat-resistant articles, while lower temperatures and longer periods are used for sensitive materials. It is important that the effectiveness of any sterilizing schedule be determined under actual working conditions by means of thermocouples or other suitable indicating devices placed in representative locations within the load, and, after a proper schedule has been determined, that the chamber be loaded in substantially the same manner for all subsequent cycles in which the particular material is to be treated. Appropriate biological indicators may be employed to demonstrate the effectiveness of the sterilization cycle.

GAS STERILIZATION

Some materials can be sterilized by exposure to sterilizing gases

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[1] All temperatures herein specified are in Celsius (centigrade) degrees.

[2] F_o value is the time (in minutes) at a particular temperature ...given sterilization effect. The product microbial at...determine the minimum F_o value (the equivalent time at ...ired to provide less than 1×10^{-6} probability of survival. ...Phillips and Miller, *Industrial Sterilization*, Duke Uni... Press, 1973, pages 239-282, and *Validation of Steam ...Cycles*, Parenteral Drug Association, Inc., Technical ...No. 1, 1978.)

as ethylene oxide.[1] These gases are highly flammable when mixed with air and thus are usually diluted for use with inert gases such as carbon dioxide or suitable fluorinated hydrocarbons.

Gas sterilization requires specialized, but not necessarily elaborate, equipment designed for the particular purpose. The choice of this form of sterilization must take due account of the possible production of toxic substances resulting from the exposure to the gas. This is particularly true for the use of ethylene oxide in sterilizing articles that contain chloride ions. Ethylene oxide–sterilized products should be monitored to assure acceptable levels of residual gas and its degradation products. Because the level of humidification, heat, gas concentration, and time of exposure relate directly to the product design (including penetrability, desiccation of components, packaging system employed, and bioburden of the product), careful determinations of the appropriate cycle parameters must be made.

Monitoring of the sterilization cycle requires the employment of modern instrumentation to monitor the concentration of ethylene oxide, the temperature, the time, and the moisture content in the sterilizing chamber. Appropriate biological indicators are available initially to demonstrate and routinely to monitor the effectiveness of the sterilizing process. As with other methods of sterilization, a bioburden history of the article should be established, since this factor influences the effectiveness of the sterilization process.

STERILIZATION BY IONIZING RADIATION

Radiation techniques are available for the sterilization of appropriate articles. The choice of sterilization dose should be determined by the microbial bioburden (types and numbers) and the nature of the article to be sterilized. A dose of 2.5 Mrads frequently has been selected as a starting point, but many articles, including radiation-sensitive articles having low or susceptible bioburdens, can be sterilized effectively at lower absorbed-dose levels. As with the other sterilization processes, the effectiveness of the radiation cycle should be confirmed by a series of experimental studies and by determination of pre-sterilization bioburdens, and by the use of suitable dosimeters. Appropriate and suitable standardized biological indicators may be used also. The continued effectiveness of the determined sterilization procedure should be periodically monitored. Absorbed-dose calorimeters, and solutions of ferrous sulfate, ferrous cupric sulfate, or ceric sulfate, are employed as standards for dosimetry. Other systems are available for measurement of dose and dose distribution in products through the color change that radiation causes in these indicators. There are also nonquantitative exposure indicators.

The practical sources of radiation are electron accelerators and radioisotopes. Electron accelerators produce high-energy electrons with a low penetrating ability, and their use requires careful control of many variables affecting sterilization efficiency. Among these variables are electron energy, electron current, scan width, exposure time, and product density. Radioisotope sources, such as ^{60}Co and ^{137}Cs, have been employed for sterilization purposes. The ^{60}Co isotope is currently the most widely used source of gamma radiation.

STERILIZATION BY FILTRATION

This process, which depends upon the physical removal of organisms by adsorption on the filter medium or by a sieving mechanism, is used for the sterilization of heat-sensitive solutions. Microbial bioburdens of solutions to be filtered should be determined as part of validation and monitoring, since the effectiveness of the filtration procedure can be greatly influenced by the microbial load in the solution to be filtered.

Filter media vary in form and composition. A suitable filter yields a sterile and relatively particle-free filtrate and does not alter essentially the composition of the fluid passing through it. In practice, the filter, receiving vessel, and any required accessories are sterilized by a suitable means determined by the nature of the components in the system. The solution to be treated is then passed through the filter and collected in the sterile receiver by the application of positive pressure to the non-sterile side of the system or application of vacuum to the sterile side. Care must be taken to avoid excessive positive or negative pressure, which may lead to failure of the sterilization process. Prolonged filtration must be avoided also, lest a contaminant grow through the filter medium and enter the sterile solution.

The integrity of any new or modified filtration system should be determined before it is placed in service, and all filter elements of porcelain, diatomaceous earth, or sintered material that are used repeatedly should be tested for cracks or leaks prior to each use. Fiber-shedding filters are to be avoided unless it has been demonstrated that elimination of the fiber-shedding filter results in additional safety risk or adversely affects the efficacy of the product. Where a fiber-shedding filter is retained, an additional nonfiber-shedding filter must be introduced downstream in the system. Suitable tests should be developed to test the integrity of a filtration unit employing membrane filters after the filtration process has been completed.

Biological Indicators

Biological indicators are standardized preparations of specific microorganisms relatively resistant to the particular sterilization process, used to demonstrate in a positive manner the adequacy of the sterilization process. They are of two forms, each of which incorporates a viable culture of a known species of microorganism. In one form, the culture is added to representative units of the lot to be sterilized; if the use of this form is not practicable, an alternative is required, in which the culture is added to disks or strips of filter paper or metal, or glass or plastic beads. It is preferable that the carrier of the biological indicator be as similar as possible in composition to the package or item being sterilized. If the material to be sterilized is a liquid, and if it is not practicable to add a biological indicator to selected units of the lot, the viable culture may be added to a simulated product that offers no less resistance to sterilization than the product to be sterilized.

The effective use of biological indicators for the monitoring of a sterilization process requires a thorough knowledge of the product being sterilized and its component parts (materials and packaging), and of the probable types and numbers of microorganisms constituting the microbial bioburden in the product immediately prior to sterilization. The selection of a satisfactory biological indicator is critical, and requires that due weight be given to a knowledge of the resistance of the microorganism incorporated in it to the specific sterilization process to be monitored. While a microorganism may be highly resistant to one sterilization process, it may not necessarily be suitable for monitoring other sterilization processes. Consideration must be given also to that form (spore or vegetable cell) which is appropriate to the particular sterilization process being employed. A satisfactory biological indicator demonstrates that, when used within its performance characteristics, the challenge to the sterilization process exceeds the challenge of the natural bioburden. Also, biological indicators must be properly standardized so that the biological indicator units in the lot all exhibit the same degree of resistance to the sterilization process when used in the same manner even if varying at different times within the dating period of the biological indicator.

The particular biological indicator used should be selected not only with respect to the manner in which it is used in or upon the product being sterilized, but also with respect to the choice of sterilization method. For steam sterilization at certain temperatures, spores of suitable strains of *Bacillus stearothermophilus* are widely employed because of their resistance to this type of sterilization. For dry-heat or ethylene oxide sterilization, spores of suitable strains of *Bacillus subtilis* are preferable. Spores of suitable strains of *Bacillus pumilus* are utilized as biological indicators to monitor sterilization processes using gamma or other ionizing radiation.

The preparation of stock suspensions of selected microorganisms requires competence in the techniques for maintaining and standardizing the microbial cultures. Where spore suspensions are used to prepare a biological indicator, it is important that the stock suspension contain predominantly spores that have been held in a non-nutritive liquid. Precautions are necessary to ensure that the biological indicator inoculum contains no substances that substantially alter the resistance of the indicator organisms to the sterilization process.

It is important that the biological indicator preparations commercially available maintain their label concentration of viable spores or cells throughout the dating period, since the performance of the biological indicator is a function of its initial viable count as

[1] See Ethylene Oxide, Encyclopedia of Industrial Chemical Analysis, 12: 317–340, John Wiley & Sons, Inc., and *Use of Ethylene Oxide as a Sterilant in Medical Facilities*, NIOSH Publication No. 77-112, December 1976, Occupational Hazard Review with Control Recommendations, August 1977, U. S. Department of Health, Education and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, Division of Criteria Documentation and Standards Development, Priorities and Analysis Branch, Rockville, MD

well as the resistance of each viable unit or cell. Preparations made by the user should have equivalent properties.

Labeling for commercially prepared biological indicators should include the following information: lot number, expiration date, preferred storage conditions, performance characteristics such as D values[4] under given sterilization parameters, directions for use (including required recovery medium and incubation conditions), and recommendations for disposal. Performance characteristics of some biological indicators are given in the accompanying table.

Typical Performance Characteristics of Some Biological Indicators

Culture	Sterilization Process	Approximate D Value
Bacillus subtilis spores	Ethylene oxide, at 50% relative humidity and 54°	
	600 mg per liter	3 minutes
	1200 mg per liter	1.7 minutes
Bacillus stearothermophilus spores	Saturated steam at 121°	1.5 minutes
Bacillus pumilus spores	Gamma radiation	
	Wet preparations	0.2 Mrad
	Dry preparations	0.15 Mrad
Bacillus subtilis spores	Dry heat at 121° to 170°	60 minutes to 1 minute
Clostridium sporogenes spores	Saturated steam at 112° to 121°	3.5 minutes to 0.7 minute

Aseptic Processing Areas

The primary objective of aseptic processing is to prevent the introduction of microbial contamination during the handling of materials. The principal sources of contamination are the air and water in the area and the personnel, materials, and equipment involved in the processing.

Proper environmental control depends upon microbiological barriers. Design features that make use of the double barrier include hoods, cabinets, or other types of enclosures that serve as the primary barrier around the process, and the room itself, which serves as a secondary barrier.[5] Other important engineering features include:

(1) The choice of materials for walls, floors, and ceilings that result in nonporous surfaces and freedom from crevices, ledges, and unnecessary projections.

(2) Maintenance of differential positive air pressures to prevent inward leakage of air.

(3) Effective filtration of air supplied to the primary and secondary barriers.

(4) Provision of air locks at the entrances to rooms.

(5) An effective intercommunication system and a suitable room arrangement to minimize traffic. An appropriate program should be established initially to qualify aseptic areas and equipment and routinely to monitor the integrity of the measures.

The primary barrier for an aseptic processing operation may be absolute or partial. An absolute barrier allows no interchange of the protected and unprotected environments and usually consists of a gas-tight enclosure constructed of stainless steel, with the processing operations being done through attached arm-length rubber gloves or by remotely controlled machinery. Such a barrier enclosure should be maintained at a positive pressure.

A partial barrier cabinet allows some interchange of the protected and unprotected environments and depends upon an outward or downward flow of clean air to prevent ingress of contamination. Enclosed benches with laminar flow of air filtered through high-efficiency particulate air filters are examples of partial barrier equipment.

Personnel, materials, and equipment entering aseptic processing rooms constitute a major source of contamination. The use of sterile caps, masks, gowns, gloves, and shoe covers by personnel is effective in reducing the hazard from this source. Problems concerning materials and equipment are peculiar to each situation and require specific attention. In all cases, traffic should be minimized and visitors should not be permitted in areas where aseptic processing is conducted.

One of the most important aspects of the control of environmental contamination in aseptic processing areas is the daily janitorial care and maintenance of the areas. Ideally, the cleaning and maintenance should be done after the completion of each day's work so that the rooms remain unoccupied for some time, preferably overnight, before the next operation is started.

In connection with any aseptic filling, it is important to determine the effectiveness of the precautionary measures used to minimize microbial contamination. Particulate matter and microbial air samplers should be employed to monitor the working area during active periods.

One suggested satisfactory positive general check on the entire filling operation may be obtained by processing, under routine conditions, the equivalent of a representative lot of containers, filling them with a suitable sterile culture medium, incubating the entire lot, and examining for the presence of contamination. Records established as a result of conducting this type of test at intervals serve as an important adjunct to the results of sterility tests on the finished product (see *Sterility Tests* ⟨71⟩).

Sterility Testing of Lots

The attainment of sterility in a lot of Pharmacopeial articles purporting to be sterile is dependent on the microbiological condition of the components of the product prior to formulation and the effectiveness of the sterilization or decontamination procedures. The sterility test of the lot of finished dosage forms described in the first four paragraphs under *Sterility Tests* ⟨71⟩ serves as one indication of the sterility of the lot. It is recognized that sterility tests may not detect microbial contamination of a low order of magnitude in a lot of product. The sterility test (see ⟨71⟩) is intended as the official referee test in the event that a dispute arises concerning the sterility status of the lot under certain conditions as discussed below. The statistical limitations of the sampling requirements given in the section, *Selection of Test Specimens*, under *Sterility Tests* ⟨71⟩ are clear, but this inherent limitation must be accepted since the current state of the art does not permit non-destructive tests to determine the microbiological condition of every container of a lot of finished dosage forms.

Sterility test procedures sometimes are used to monitor in-process manufacture, in which case they may be modified from the official test described, and appropriate sampling plans employed. Negative results from a valid sterility test are indicative of the sterility of the lot only if the records of all pertinent sterilization or microbiological decontamination procedures and aseptic processing stages subsequent to sterilization indicate that these processes have been carried out in complete accordance with the written standard operating procedures in the manufacturer's files, and that these are in compliance with current compendial and regulatory requirements and principles for the production of Pharmacopeial products.

Sampling of small lots.—For sterility test purposes the two basic considerations that influence the sterility sampling plans and test patterns are the filling operation and the sterilization procedure. For aseptic fills, the term "filling operation" describes a group of final containers, identical in all respects, that have been aseptically filled with the same product from the same sterile bulk within a period of time not longer than 24 consecutive hours without any interruption or change that affects the integrity of the filling assembly. For such fills, if more than three filling machines, each with either single or multiple filling stations, are used for filling a

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[4] The D value is the exposure under the particular sterilization conditions to reduce the microbial population by 90%. For heat sterilization, the D value is the thermal resistance value (in minutes) to reduce the microbial population by 90% at the specified temperature (see also Footnote 2).

[5] Available published standards for such controlled work areas include the following: (1) Federal Standard No. 209B, Clean Room and Work Station Requirements for a Controlled Environment, Apr. 24, 1973. (2) NASA Standard for Clean Room and Work Stations for Microbially Controlled Environment, publication NHB5340.2, Aug. 1967. (3) Contamination Control of Aerospace Facilities U.S. Air Force, T.O. 00-25-203 1 Dec. 1972, change 1 1 Feb. 1974. To monitor aseptic processing areas where viable microbial standards have been established (rather than total particulate standards) appropriate measures, such as agar-plate exposure devices rather than particle counters), should be

...ing machine, but the total number generally need not exceed ...ntainers. The items tested should be representative of each ... assembly and should be selected at appropriate intervals ...hout the entire filling operation.

...rticles may be terminally sterilized either in a chamber or by ...tinuous process. In the chamber process, a number of articles ...erilized simultaneously under controlled conditions, e.g., in ...autoclave, so that for the purpose of sterility testing, the lot ...sidered to be the contents of a single chamber. In the con... process, the articles are sterilized one by one, e.g., as by ...sure to penetrating radiation, so that the lot is considered to ...not larger than the total number of similar items subjected to ...uous sterilization for a period of not more than 24 hours.

...the case of either aseptic filling or terminal sterilization, if the ...ber of final containers in the sterility test lot is between 20 and ...not fewer than 10% of the containers usually should be tested. ...the number of final containers in the lot is 20 or less, not fewer ...final containers should be tested.

...erility tests are highly exacting and should be conducted by ...nnel who have had either training in microbiology or experi... with rigid aseptic techniques. Responsibility for (a) the se... of test procedures and controls to be used, (b) the interpre... of test results, and (c) the final decision to accept or reject ...ch reasons pertaining to sterility should rest upon a person who ...s had training in microbiology and who has a knowledge of the ...principles of sterilization processes and an understanding of ...statistical limitations of sampling. It is therefore imperative ...the responsible personnel be kept informed of any modifications ...changes in or contemplated for established manufacturing pro... including sterilization and packaging.

...The sterility test facility should be designed to include laboratory ...surfaces that are serviced by a suitable filtered air supply such ...with high-efficiency particulate air filters supplied to the work ...a laminar flow pattern (see footnote 5).

...The area in which sterility tests are conducted should be subject ...environmental control so as to be as free as practicable from dust ...borne microorganisms. The regular use of monitoring ...ces such as microbial air-samplers is an effective aid to this ...To reduce the hazard of adventitious contamination, ad... to the testing area should be limited to personnel who are ...ified and whose presence is required. Dust and other ...traneous matter should be removed from all equipment ...the samples to be tested, prior to transfer into the imme... testing area, and suitable controls should be included to verify ...efficacy of the testing apparatus to be used. Sterility tests should ...be conducted under direct exposure to artificial ultraviolet light ...area undergoing germicidal aerosol treatment. Air-pres... differentials should be maintained to supply air pressure to the ...area that is positive to adjoining areas, including equipment ...and gowning rooms.

Sterile Pharmaceutical Products—Because of rapid ra... decay, it is not feasible to delay the release of some ra... pharmaceutical products in order to complete sterility tests ...In such cases, early release of such products for use is ...permissible, provided that (a) the manufacturer has ...that the methods of manufacture and sterilization em... adequate insofar as the sterility of each final product is ...and (b) the manufacturer uses appropriate sterility test ...on each lot manufactured, as additional evidence of the ...methods of manufacture and sterilization.

⟨1221⟩ TEASPOON

...household purposes, an American Standard Teaspoon has ...established by the American National Standards Institute* ...ing 4.93 ± 0.24 ml. In view of the almost universal ...employing teaspoons ordinarily available in the house... the administration of medicine, the teaspoon may be re... representing 5 ml. Preparations intended for adminis... spoon should be formulated on the basis of dosage in ...dropper, syringe, medicine cup, special spoon, or ...teaspoon. Any dropper, syringe, medicine cup, special spoon, or ...used to self-measure liquids should deliver 5 ml wherever ...calibration is indicated. Under ideal conditions of use, ...error incurred in measuring liquids for individual dose ...by means of such calibrated devices should be not ...than 10% of the indicated amount.

...units are used often to inform the patient of the size ...of the dose. Fifteen milliliters should be considered 1 tablespoonful, 10 ml, 1 dessertspoonful; and 5 ml, 1 teaspoonful. Doses of less than 5 ml are frequently stated as fractions of a teaspoonful or in drops.

Because of the difficulties involved in measuring liquids under normal conditions of use, household spoons are not appropriate where accurate dosage is required. It must be kept in mind that the actual volume of a spoonful of any given liquid is related to the latter's viscosity and surface tension, among other influencing factors. These factors also cause variability in the true volumes contained in or delivered by medicine cups. Where accurate dosage is required, a calibrated syringe or dropper should be used.

⟨1231⟩ WATER FOR PHARMACEUTICAL PURPOSES

Inasmuch as water is used more copiously and widely than any other substance in pharmaceutical manufacturing, its quality is of the utmost importance. Adequate control over the quality of the water supply involves exceptional difficulties, since the basic source, usually a municipal system, is influenced by many and varied factors. With respect to variations in the two most important attributes, the content of solids and of microorganisms, respectively, it is a possible change in the latter that calls for the closest surveillance.

Water—Water is required for a variety of purposes ranging from the needs of manufacturing processes to the final preparation of therapeutic agents just prior to their administration to patients. Hence the Pharmacopeia provides several monographs for water, as follows.

Drinking water, which is subject to the federal Environmental Protection Agency regulations with respect to drinking water, and which is delivered by the municipal or other local public system or drawn from a private well or reservoir, is the starting material for all forms of water covered by Pharmacopeial monographs. Drinking water may be used in the preparation of USP drug substances but not in the preparation of dosage forms, or in the preparation of reagents or test solutions.

Purified Water (see USP monograph)—This article represents water rendered suitable for pharmaceutical purposes by distillation, by ion-exchange treatment (deionization or demineralization), by reverse osmosis, or by other suitable process. It meets rigid specifications for chemical purity. It meets the requirements of the federal Environmental Protection Agency with respect to drinking water, and it contains no added substance. However, the various methods of production present considerably different possibilities for contamination. Purified Water produced by distillation is sterile, provided the condenser is sterile. On the other hand, ion-exchange columns and reverse osmosis units require special attention in that they afford sites for microorganisms to lodge, to multiply, and to enter the effluent. Thus, frequent monitoring may be called for, particularly with the use of these units following periods of shutdown of more than a few hours.

Water for Injection (see USP monograph)—By definition, this article is water purified by distillation or by reverse osmosis, and it meets the purity requirements under *Purified Water*. It need not be sterile, but, in order to meet a test for freedom from pyrogens, it must be produced, stored, and distributed in such a way that microorganisms, if present, do not produce pyrogens.

Sterile Water for Injection (see USP monograph)—As a form in which water is distributed in sterile packages, Sterile Water for Injection is intended mainly for use as a solvent for parenteral products such as sterile solids that must be distributed dry because of limited stability of their solutions. It is subject to the limitation that it may be packaged only in single-dose containers of not larger than 1-liter size.

Bacteriostatic Water for Injection (see USP monograph)—Inasmuch as it serves the same purposes as Sterile Water for Injection, it meets the same standards, with the exception that it may be packaged in either single-dose or multiple-dose containers of not larger than 30-ml size.

Sterile Water for Irrigation (see USP monograph)—This form of water meets the same requirements as for Sterile Water for Injection, except with respect to (1) container size (i.e., the container may contain a volume of more than 1 liter of Sterile Water for Irrigation), and (2) the *Labeling* requirements (e.g., the designations "For irrigation only" and "Not for injection" appear prominently on the label).

* American National Standard Institute, 1430 Broadway, New York

ANEXO 3

Anexo 3

INVERSION EN EQUIPOS Y DOTACION GENERAL

	U N I D A D	V.UNITARIO ($)	No.	TOTAL
1	FILTRO DE ARENA Metálico con conexiones en PVC cilindro vertical. Capacidad 6 pies^3 (016" x 48") con regeneración 0.2 Kw.	40.000	1	40.000
2	TANQUE ALMACENAMIENTO AGUA FILTRADA En poliester reforzado con fibra de vidrio e = 7.1 mm. Capacidad 1.700 G-cilindro horizontal. Manhole e indicador de nivel	100.000	1	100.000
3	ABLANDADOR Metálico con conexiones en PVC. Capacidad: 3-10 GPM (14' x 72"). Sistema de regeneración 0.2 Kw.	99.000	1	99.000
4	TANQUE ALMACENAMIENTO AGUA BLANDA En polietileno A.densidad e = 6 mm. Capacidad 500 G-cilindro vertical. Manhole e indicador de nivel	20.000	2	40.000

Anexo 3: CONTINUACION

	UNIDAD	V.UNITARIO ($)	No.	TOTAL
5	DEIONIZADOR Cuerpo metálico, conexiones en PVC. Dos columnas. Capacidad 1.5-6 GPM. (14"x48"). Sistema de regeneración 0.2 Kw. 250.	80.000	1	80.000
6	TANQUE ALMACENAMIENTO AGUA DEIONIZADA Polietileno de A.Densidad e= 6 mm. Capacidad 1.500 L. Cilindro vertical. Manhole e indicador de nivel	20.000	2	40.000
7	OSMOSIS INVERSA Con dos cartuchos de microfiltración de 50". Milli-RD-250. Capacidad 80 LPH. Carcazas en acero inoxidable. Montaje adosado a un muro o soporte 5.7 AMP. 220-250V-60Hz.	180.000	1	180.000
8	TANQUE ALMACENAMIENTO AGUA PARA IN- YECCION Acero inoxidable 316 e= 3 mm. con sa- lidas. Pulido 180. Capacidad 800 lt.			

Anexo 3: CONTINUACION

	U N I D A D	V.UNITARIO ($)	No.	TOTAL
	cilindro vertical. Con patas de 0.50 m de alto	160.000	2	320.000
9	MEZCLADOR Acero inoxidable 316 con agitador, bafles y salidas Pulido 180. Capacidad de 110 lt. cilindro vertical 1/4 HP. Montado sobre plataforma de 1.5 m de alto.	110.000	1	110.000
10	TANQUE ALMACENAMIENTO SOLUCIONES Acero inoxidable 316 con salidas. Pulido 180. Capacidad 110 lt. cilindro vertical. Con patas de 0.50 m de alto	70.000	3	210.000
11	PRE-FILTRO Cartucho de 22 micrones CE 31". Montado en soporte adosado a la pared	30.000	1	30.000
12	FILTRO ESTERIL Cartucho de 22 micrones.Duraporte 10" Montado en soporte adosado a la pared	30.000	1	30.000

Anexo 3: CONTINUACION

	U N I D A D	V.UNITARIO ($)	No.	TOTAL
13	LINEA ENVASADO			
	Mesa distribución en S.S., tapa giratoria 1/4 HP	90.000	1	90.000
	LLenadora Vr.520. Dos jeringas, max. 600 cc. Capacidad 9 botellas pm. 1/3 HP.	320.000	1	320.000
	Tapadora. Montada en Vr.520 1/4 HP. Capacidad Max.60 Bot. pm.	290.000	1	290.000
	Selladora. Montado sobre mesa 1/4 HP. Capacidad max.30 botella pm.	105.000	1	105.000
14	FLUJO LAMINAR			
	Módulos suspendidos para conexión a ductos de aire acondicionado con fil tros HEPA 1/3 HP.	100.000	2	200.000
15	PRELAVADO ENVASES RE-USADOS			
	Enjuague con solución de Na Oll en tanque de SS.	30.000	1	30.000
16	LAVADORA DE ENVASES			

Anexo 3: CONTINUACION

	U N I D A D	V.UNITARIO ($)	No.	TOTAL
	Rotatoria continua 1/4 HP. 1 estación externa, 8 estaciones internas. 10 espacios para botellas. Máquina con toberas y soportes	200.000	1	200.000
17	CALENTADOR AGUA BLANDA Intercambiador de tubos y carcaza en S.S. calentamiento con vapor	20.000	1	20.000
18	FILTRO PARA VAPOR Soporte de S.S. y filtro de disco 10 micrones O 293 mm. Conectado a la línea de vapor	60.000	2	120.000
19	FILTRO PARA AIRE Soporte de S.S. y filtro de disco. 22 micrones O 90 mm. Conectado a la línea de aire.	10.000	1	10.000
20	ESTERILIZADOR Rectangular Bulk. Single Door Cabinet- 2 Kw. Cámara 8" x 12" x 20" Producto	700.000	1	700.000

Anexo 3: CONTINUACION

	U N I D A D	V.UNITARIO ($)	No.	TOTAL
21	ESTERILIZADOR Rectangular Bulk.Double Door Recesseed one end. 2 Kw. Cámara 8" x 12" x 20" Producto utensilios a estéril	853.000	1	853.000
22	FILTRO PARA CONDENSADO Soporte en S.S. y filtro de disco de profundidad 5 micrones conectado a descarga de condensado del esterilizador.	10.000	1	10.000
23	CANASTILLAS PARA ESTERILIZACION En alambre de S.S. 25 x 75 x 55. Carga del esterilizador 6 canastillas x 35 botellas	2.000	20	40.000
24	SOPORTES PARA CARGA A ESTERILIZADOR En ángulos S.S. 1" x 1" x 1/8, de 3 gavetas.	12.000	4	48.000
25	ETIQUETADORA Instalado en transportador 1/4 HP.	30.000	1	30.000

Anexo 3: CONTINUACION

	U N I D A D	V.UNITARIO ($)	No.	TOTAL
26	TRANSPORTADORA A INSP. ETIQ. Y EMPAQUE Mesa metálica con banda transportadora 1/2 HP.	40.000	1	40.000
27	TRANSPORTADOR ENVASES AZ.ESTERIL Mesa en SS con banda transportadora 1/4 HP	15.000	1	15.000
28	TRANSPORTADOR SOLUCIONES A SELLADORA Mesa en SS con banda 1/4 HP	10.000	1	10.000
29	MESA ACUMULADORA En SS mesa giratoria 1/4 HP	90.000	1	90.000
30	LAVADORA DE TAPONES DE CAUCHO Con ciclos de lavado 1/3 HP	15.000	1	15.000
31	SUBESTACION ELECTRICA Transformador 100 Kw con controles	500.000	1	500.000
32	COMPRESOR DE AIRE Capacidad 8.8 CFM-100 psi. tanque 30 G - 2 HP	18.000	1	18.000

Anexo 3: CONTINUACION

	U N I D A D	V.UNITARIO ($)	No.	TOTAL
33	CALDERA Horizontal 20 BHP-150 psi para ACPM 12,1 GPH. 2 HP	500.000	1	500.000
34	TANQUE PARA COMBUSTIBLE En acero, para ACPM. Cap. 1.500 G. cilindro horizontal sobre bases de concreto	70.000	1	70.000
35	TALLER DE REPARACIONES Equipo nuevo de maq. herramientas	200.000	1	200.000
36	INSTRUMENTACION ADICIONAL Controles de nivel para tanques agua filtrada, agua blanda, agua desionizada y agua para inyección	20.000	4	80.000
37	BOMBAS PARA MANEJO DE LIQUIDOS Agua filtrada al ablandador y lavadora. Fundición 1/4 HP 1.8 GPM a 40 psi	5.000	2	10.000
	Agua filtrada al desionizador fundi-			

Anexo 3: CONTINUACION

U N I D A D	V.UNITARIO ($)	No.	TOTAL
ción 1/4 HP	9.000	1	9.000
Agua blanda a enf. esterilizador y lavadora. Bronce, 1/4 HP - 1.8 GPM 40 psi.	9.000	2	18.000
Agua para inyección a mezclador. SS. 304, 3/4 HP	20.000	1	20.000
Agua para inyección a lavadora y ent Juagues. SS. 304, 3/4 HP 1 1/4-3/4	20.000	1	20.000
Solución a envasadora x filtros. SS. 304, c/4 HP	20.000	1	20.000
Rechazo de lavadora 2 al 1 fundición 1/4 HP	5.000	1	5.000
Rechazo de lavadora. Est.3 a 7 y ext. a tanque agua filtrada fundición,1/4 HP	5.000	1	5.000
38 MATERIALES Y EQUIPOS PARA DOTACION	300.000	1	
Balanza para reactivos	70.000	1	
Báscula			

Anexo 3: CONTINUACION

	U N I D A D	V.UNITARIO ($)	No.	TOTAL
	Estantería y mesas de trabajo	300.000	1	
	Aspiradora industrial	220.000	1	
	Elementos de limpieza	60.000	1	
	Vestuario general	90.000		
	Utensilios de trabajo SS.	300.000		
	Transporte interno	100.000		
	Otros elementos	100.000		1'540.000
39	DOTACION DE OFICINAS ADMINISTRATIVAS			
	Escritorios y sillas	220.000		
	Archivadores y mesas	80.000		
	Máquinas de oficina	160.000		
	Elementos de trabajo	100.000		560.000
40	DOTACION Y ELEMENTOS PARA LABORATORIO			
	CONTROL DE CALIDAD	750.000	1	
	Balanza de precisión	800.000	1	
	Autoclave	35.000	1	
	Planchas	640.000	1	
	Microscopio	450.000	1	
	Incubadora	350.000	1	
	Horno			

Anexo 3: CONTINUACION

U N I D A D	V.UNITARIO ($)	No.	TOTAL
Mufla	400.000	1	
Ph metro	10.000	1	
Refrigerador	70.000	1	
Material de vidrio	500.000		
Reactivos y medios de cultivo	250.000		
Unidad para control de esterilización	92.000		
Otros	300.000		4'647.000
T O T A L			12'742.000

Anexo 4

REQUERIMIENTOS DE PERSONAL

CARGOS Y/O ACTIVIDADES	CANTIDAD	SALARIO MES
PERSONAL DE PRODUCCION		
- Jefe de Producción		
Químico Farmacéutico responsable técnico de la producción	1	41.150
- Supervisores de Producción		
Mando medio para las funciones de:		
1 Control sobre el área de tratamiento agua, esterilización y empaque, caldero	1	32.140
2 Control sobre preparación de envases, área estéril y asépticos.	1	13.900
- Mecánico de mantenimiento, con especialización a nivel intermedio en mecánica general	1	15.150
- Electricista de mantenimiento, con especialización a nivel intermedio en instalaciones eléctricas	1	13.900
- Transporte interno. Con nivel de educación secundaria y experiencia de trabajo	1	13.900
- Operarios en área estéril. Con nivel de edu-		

ANEXO 4

Anexo 4

REQUERIMIENTOS DE PERSONAL

CARGOS Y/O ACTIVIDADES	CANTIDAD	SALARIO MES
PERSONAL DE PRODUCCION		
- Jefe de Producción Químico Farmacéutico responsable técnico de la producción	1	41.150
- Supervisores de Producción Mandos medios para las funciones de:	1	10.700
1 Control sobre el área de tratamiento agua, esterilización y empaque, caldera	1	32.140
2 Control sobre preparación de envases, área estéril y aséptica.	1	13.900
- Mecánico de mantenimiento, con capacitación a nivel intermedio en mecánica general	1	15.150
- Electricista de mantenimiento, con capacitación a nivel intermedio en instalaciones eléctricas	1	13.900
- Transporte interno. Con nivel de educación secundaria y experiencia de trabajo	1	13.900
- Operarios en Area Estéril. Con nivel de edu-		

Anexo 4: CONTINUACION

CARGOS Y/O ACTIVIDADES	CANTIDAD	SALARIO MES
cación secundaria y experiencia de trabajo.	1	13.900
- Operario y ayudantes de preparación de soluciones con nivel de educación secundaria	1	13.900
- Operario y ayudantes en lavado y preparación envases, con nivel de educación secundaria	1	10.700
- Operarios y ayudante de selladora con nivel de educación secundaria	1	10.700
- Operarios y ayudantes en esterilización, inspección y empaque, con nivel de educación secundaria $10.700 c/u.	2	21.400
- Operarios de caldera y equipo de tratamiento de agua, con nivel de educación de secundaria y experiencia de trabajo	1	13.900
TOTAL	13	214.640

Anexo 4: CONTINUACION

CARGOS Y/O ACTIVIDADES	CANTIDAD	SALARIO MES
PERSONAL DE CONTROL DE CALIDAD		
- Jefe de control de calidad, químico Farmacéutico, responsable del cumplimiento de las normas de calidad del producto, análisis de materias primas, producto, etc.	1	41.150
TOTAL	1	41.150
PERSONAL DE ALMACENES: MATERIALES Y PRODUCTO		
- Jefe de almacén, con nivel de educación secundaria, responsable de los inventarios.	1	21.300
- Ayudantes de almacén	1	13.900
TOTAL	2	35.200
PERSONAL ADMINISTRATIVO	1	55.450
- Gerente-Administrador	1	21.300
- Jefe Contabilidad	1	13.900
- Auxiliar Contabilidad		

Anexo 4: CONTINUACION

CARGOS Y/O ACTIVIDADES		CANTIDAD	SALARIO MES
- Secretarias $17.250 c/u		2	34.500
TOTAL		5	125.150
PERSONAL SERVICIOS GENERALES			
- Conductores $10.700 c/u		2	21.400
- Aseadoras $10.700 c/u		2	21.400
- Coladores $10.700 c/u		3	32.100
TOTAL		7	74.900
	%		
PERSONAL DE PRODUCCION M.O.D.	43.7	13	214.640
PERSONAL CONTROL CALIDAD M.O.I.	8.3	1	41.150
PERSONAL ALMACEN Personal Administ.	7.2	2	35.200
PERSONAL ADMINISTRATIVO Pers.Adm.	25.5	5	125.150
PERSONAL SERVICIOS GRALES. M.O.I.	15.3	7	74.900
TOTAL MENSUAL	100%	28	491.040

PLANTA PRODUCTORA DE DEXTROSAS Y SIMILARES

CALCULO DE PRESTACIONES PARA FUNCIONARIOS

AÑO 1983

BONIFICACION

$$\frac{\text{S. Básico Mensual}}{4} = \frac{491.040}{4} = 122.760 = 122.760$$

PRIMA SERVICIOS

$$\frac{\text{S. Básico + Bonificación + Aux.Transporte + S.Alimentación}}{2}$$

$$\frac{491.040 + 122.760 + 17.820 + 22.800}{2} = \frac{654.420}{2} = 327.210$$

PRIMA VACACIONES

$$\frac{\text{S. Básico + Bonificación + Aux.Transporte + S.Aliment. + } \frac{\text{P.Servicios}}{2}}{2}$$

$$\frac{491.040 + 10.230 + 17.820 + 22.800 + 27.268}{2} = 569.158/2 = 284.579$$

PRIMA NAVIDAD

$$\text{S.Básico} + \frac{\text{P.Serv.}}{12} + \frac{\text{P.Vacac.}}{12} + \frac{\text{Bonif.}}{12} + \text{S.Aliment.} + \text{Aux.Transporte}$$

$$491.040 + 27.268 + 23.715 + 10.230 + 17.820 + 22.800 = 592.873$$

CESANTIAS

S. Básico + $\frac{\text{P.Nav.}}{12}$ + $\frac{\text{Dominic.y Fest.}}{12}$ + S.Aliment. + Aux.Transporte

+ Bonif. + P.Serv. + P.Vacac.

491.040 + 49.406 + 22.800 + 17.820 + 10.230 + 27.268 + 23.715 =

642.279

SUELDO MENSUAL

491.040 x 12 = 5'892.480

ANEXO 5

TOTAL AÑO: $7'862.181.

N o t a : El salario incluye la Prima de Antiguedad.

Aux.Transporte $810 por funcionario hasta salarios

$18.220. # 22 Total mes $17.820.

Sub. Alimentación $950 por funcionario hasta salarios

$29.200 # 24 Total mes $22.800.

FUENTE: Esta investigación.

A N E X O 5

- FACTIBILIDAD DEL MONTAJE DE UNA PLANTA -

- DE ELECTROLITOS -

Con el deseo de montar una planta de electrolitos (Dextrosas, sueros y similares) que atienda las necesidades de suministro de estos productos en el Departamento de Nariño, se está recolectando información sobre consumo, proveedores, adquisición, transporte, almacenamiento y capacidad financiera de las entidades de salud privadas y oficiales que brindan servicios de hospitalización y urgencias.

Se solicita su colaboración en el sentido de responder con exactitud las preguntas planteadas a continuación.

Muchas gracias.

- C U E S T I O N A R I O -

C O D I G O : _____

FECHA DE DILIGENCIAMIENTO: _____

I.- P A R T E :

I D E N T I F I C A C I O N

1.1. ENTIDAD _____

1.2. CARGO DEL FUNCIONARIO QUE DILIGENCIA EL CUESTIONARIO : _____

1.3. CLASE DE ENTIDAD:

VINCULADA _____ ADSCRITA _____

PROPIA DEL SISTEMA _____

PRIVADA _____ OFICIAL _____

1.4. SERVICIOS QUE PRESTA:

HOSPITALIZACION _____

URGENCIAS _____

CONSULTA EXTERNA _____

1.5. NUMERO DE CAMAS:

HOSPITALIZACION _____

OBSERVACION _____

II - PARTE

- CONSUMO -

2.1.- INFORMACION MENSUAL DE CONSUMO Y PRECIO UNITARIO PROMEDIO.-

CODIGO.-	PRODUCTO	C O N S U M O										TOTAL CANTIDADES.-
		1.977		1.978		1.979		1.980		1.981		
		Cant.-	P.Unit.	Cant.	P.Unit.	Cant.	P.Unit.	Cant.	P.Unit.	Cant.	P.Unit.	
1	Agua esteril para inyección de 1 ml. ampolla.											
2	Agua esteril para inyección de 3 ml. ampolla.											
3	Agua esteril para inyección de 5 ml. ampolla.											
4	Dextrosa 5% en A.D. soluc.iny. x 500 ml.											
5	Dextrosa 5% en A.D. soluc.iny. x 1.000 ml.											
6	Dextrosa al 5% + cloruro de sodio 0.45 sol.iny. x 500 ml.											
7	Dextrosa al 5% + cloruro de sodio 0.9% sol.iny. x 500 ml.											
8	Dextrosa al 5% + cloruro de sodio 0.9% soluc.iny. de 1.000ml.											
9	Dextrosa al 10% en A.D. soluc. iny. x 500 ml.											
10	Dextrosa al 10% en S.S. soluc. iny. x 500 ml.											
11	Dextrosa al 33% en A.D. soluc. iny. x 250 ml.											
12	Frucosa 10% soluc.iny.x 500 ml.											
13	Bicarbonato sodio sol.iny.											
14	Calcio Gluconato 10% sol.iny.											
15	Magnesio sulfato 50% sol.iny. magistral.											
16	Potasio cloruro 2 meq.sol.iny.											
17	Potasio Gluconato 31% elixir frasco.											
18	Sodio cloruro 0.9% sol.iny.											
19	Sodio cloruro 3.5 sol. iny.											
20	Sodio lactato 1/6 molar, sol. iny. x 500 ml.											

CODIGO.	PRODUCTO	C O N S U M O										TOTAL CANTIDADES.-
		1.977		1.978		1.979		1.980		1.981		
		Cant.	P.Unit.	Cant.	P.Unit.	Cant.	P.Unit.	Cant.	P.Unit.	Cant.	P.Unit.	
21	Sodio Lactado 2 molar - soluc.iny.											
22	Solución Hartman soluc. iny. x 500 ml.											
23	Solución Ringer soluc. iny. x 500 ml.											
24	Soluciones electrolíticas balanceadas con -- amortiguador.											
25	Solución para dialisis peritoneal con dextrosa al 15% sol.iny. x 500 ml.											
26	Solución para dialisis peritoneal con dextrosa al 7% sol.iny.x 500 ml.											
	NUMERO MESES INFORMADOS											

* Precio unitario promedio.-

III.- P A R T E :

P R O V E E D O R E S

3.1.- Cuenta la Entidad con Registro de Proveedores?

SI _____ NO _____

3.2.- La adquisición de los productos señalados en el cuadro NQ 2.1. se hace:

- Directamente al Laboratorio que produce?_____
- A distribuidores mayoritarios? _____
- A pequeños distribuidores? _____
- Por intermedio del Servicio Seccional de Salud?___

3.3.- Enuncie las casas comerciales a las cuales desde el ano 1.977 hasta el presente año ha comprado la entidad los- productos anotados en el cuadro NQ 2.1.

_____

_____

_____

_____

3.4.- Para la adquisición de estos productos cual cree Ud. es el mecanismo más ágil y eficáz teniendo en cuenta las - alternativas señaladas en el numeral 3.2._____

Porqué razón: _____

_____

_____

_____

_____

_____

IV.- P A R T E :

A D Q U I S I C I O N

4.1.- Para la adquisición se rige la entidad a una reglamentación legal? SI _____ NO _____

4.2.- Si contesta afirmativamente a la pregunta anterior, señale el Decreto Y/O disposición:

_____

_____

4.3.- Si la respuesta a la pregunta 4.1. es negativa indique cual es el proceso por el que se rige la Institución,- al efectuar las compras indicando en cada modalidad -- hasta que monto está autorizada la entidad para hacer- esta transacción: _____

_____

_____

_____

_____

_____

_____

_____

4.4.- Para poder determinar la adquisición de los productos- enumerados en el cuadro 2.1. que mecanismos utiliza la entidad?

- Revisión de Tarjetas de Kárdex _____
- Cantidades Máximas y Mínimas de existencia _____
- Revisión cuentas mensuales _____
- Otros mecanismos (Señale cuales) _____

_____

_____

_____

_____

4.5.- En la entidad se realiza programación anual del consumo de los productos enunciados?

SI _____ NO _____

4.6.- Con qué prioridad se realizan las adquisiciones de los productos enunciados?

Mensual _____ Bimestral _____ Trimestral_____

Semestral _____ Otras _____

_____

_____

4.7.- Si se presenta una emergencia y se carece del Producto como se procede?

_____

_____

_____

4.8.- Para la adquisición de las soluciones (Dextrosas, sueros), el personal médico y paramédico que presentación recomienda: Frasco _____ Bolsa _____ Porqué? _____

_____

V.- P A R T E :

C A P A C I D A D F I N A N C I E R A

C O N C E P T O	1.977 $	1.978 $	1.979 $	1.980 $	1.981 $
Presupuesto total de la Entidad					
Medicamentos					

VI.- P A R T E :

T R A N S P O R T E

6.1.- Los gastos de Transporte quien los asume?

- La Entidad u Organismo de Salud _____
- El Proveedor _____

6.2.- Una vez realizada la compra que tiempo promedio tardan en llegar los productos a su destino?

_____

_____

_____

_____

6.3.- Cite el nombre de tres empresas que hayan prestado el servicio a la entidad en lo que respecta a transporte de productos.

_____

_____

_____

VII.- P A R T E :

A L M A C E N A M I E N T O

7.1.- La entidad dispone de sitios específicos para el almacenaje de este tipo de producto? _____

7.2.- En el término de metros cúbicos diga el espacio destinado para el almacenamiento de los productos señalados;

_____

7.3.- Se han presentado problemas en el almacenamiento de estos productos? SI _____ NO _____

7.4.- En caso de responder afirmativamente señale cuales? _____

_____

_____

O B S E R V A C I O N E S :

Sírvase anotar las sugerencias u observaciones que estime conveniente:

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