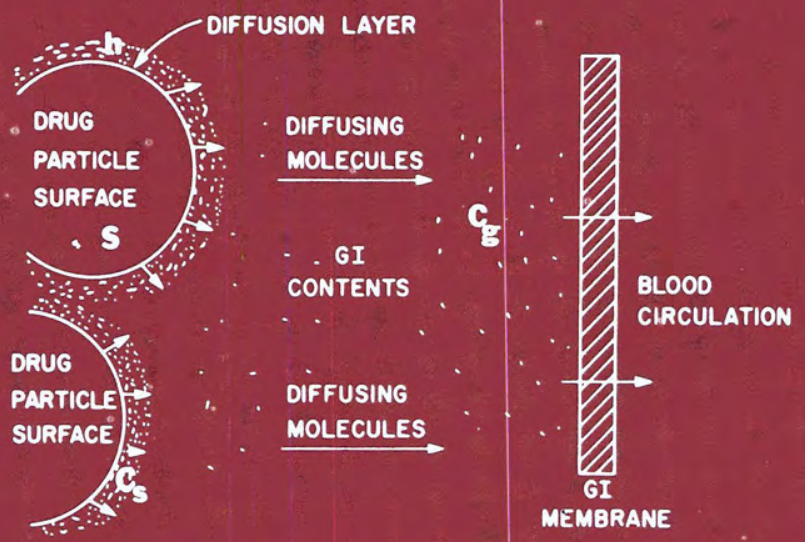
DRUGS AND THE PHARMACEUTICAL SCIENCES VOLUME 72

Modern Pharmaceutics

Third Edition, Revised and Expanded



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SUN EXHIBIT 1070, IPR2024-00107, PAGE 1

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Third Edition, Revised and Expanded

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SUN EXHIBIT 1070, IPR2024-00107, PAGE 2

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SUN EXHIBIT 1070, IPR2024-00107, PAGE 4

Contents

Preface *iii*
Contributors *vii*

1. Drug Products: Their Role in the Treatment of Disease, Their Quality, and Their Status as Drug Delivery Systems 1
   Gilbert S. Banker

2. Principles of Drug Absorption 21
   Michael Mayersohn

3. Pharmacokinetics 75
   David W. A. Bourne and Lewis W. Dittert

4. Factors Influencing Drug Absorption and Drug Availability 121
   Betty-ann Hoener and Leslie Z. Benet

5. The Effect of Route of Administration and Distribution on Drug Action 155
   Svein Øie and Leslie Z. Benet

6. Chemical Kinetics and Drug Stability 179
   J. Keith Guillory and Rolland I. Poust

7. Preformulation 213
   Jens T. Carstensen

8. Cutaneous and Transdermal Delivery: Processes and Systems of Delivery 239
   Gordon L. Flynn

SUN EXHIBIT 1070, IPR2024-00107, PAGE 5

9. Disperse Systems 299
S. Esmail Tabibi and Christopher T. Rhodes

10. Tablet Dosage Forms 333
Edward M. Rudnic and Mary Kathryn Kottke

11. Hard and Soft Shell Capsules 395
Larry L. Augsburger

12. Parenteral Products 441
James C. Boylan, Alan L. Fites, and Steven L. Nail

13. Design and Evaluation of Ophthalmic Pharmaceutical Products 489
Gerald Hecht, Robert E. Roehrs, John C. Lang, Denise P. Rodeheaver, and Masood A. Chowhan

14. Pharmaceutical Aerosols 547
John J. Sciarra

15. Sustained- and Controlled-Release Drug Delivery Systems 575
Gwen M. Jantzen and Joseph R. Robinson

16. Target-Oriented Drug Delivery Systems 611
Vijay Kumar and Gilbert S. Banker

17. Packaging of Pharmaceutical Dosage Forms 681
Donald C. Liebe

18. Optimization Techniques in Pharmaceutical Formulation and Processing 727
Joseph B. Schwartz and Robert E. O'Connor

19. Food and Drug Laws that Affect Drug Product Design, Manufacture, and Distribution 753
Garnet E. Peck

20. European Aspects of the Regulation of Drug Products 773
Brian R. Matthews

21. Pediatric and Geriatric Aspects of Pharmaceutics 809
Michele Danish and Mary Kathryn Kottke

22. Biotechnology-Based Pharmaceuticals 843
S. Kathy Edmond Rouan

23. Veterinary Pharmaceutical Dosage Forms: An Overview 875
J. Patrick McDonnell

24. A View to the Future 887
Gilbert S. Banker and Christopher T. Rhodes

Index *907*

SUN EXHIBIT 1070, IPR2024-00107, PAGE 6

12

Parenteral Products

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I. INTRODUCTION

The first official injection (morphine) appeared in the *British Pharmacopoeia* (*BP*) of 1867. It was not until 1898 when cocaine was added to the *BP* that sterilization was attempted. In this country, the first official injections may be found in the *National Formulary* (*NF*), published in 1926. Monographs were included for seven sterile glass-sealed ampoules. The *United States Pharmacopeia* (*USP*) published in the same year contained a chapter on sterilization, but no monographs for ampoules. The current *USP* contains monographs for over 400 injectable products [1].

Parenteral administration of drugs by intravenous (IV), intramuscular (IM), or subcutaneous (SC) routes is now an established and essential part of medical practice. Advantages for parenterally administered drugs include the following: rapid onset; predictable effect; predictable and nearly complete bioavailability; and avoidance of the gastrointestinal tract (GIT), and hence, the problems of variable absorption, drug inactivation, and GI distress. In addition, the parenteral route provides reliable drug administration in very ill or comatose patients.

The pharmaceutical industry directs considerable effort toward maximizing the usefulness and reliability of oral dosage forms in an effort to minimize the need for parenteral administration. Factors that contribute to this include certain disadvantages of the parenteral route, including the frequent pain and discomfort of injections, with all the psychological fears associated with "the needle," plus the realization that an incorrect drug or dose is often harder or impossible to counteract when it has been given parenterally (particularly intravenously), rather than orally.

In recent years, parenteral dosage forms, especially IV forms, have gained immensely in use. The reasons for this growth are many and varied, but they can be summed up as (a) new and better parenteral administration techniques; (b) new forms of nutritional therapy, such as intravenous lipids, amino acids, and trace metals; (c) the need for simultaneous administration of multiple drugs in hospitalized patients receiving IV therapy, (d) the extension of parenteral

SUN EXHIBIT 1070, IPR2024-00107, PAGE 7

therapy into the home; and (e) an increasing number of drugs that can be administered only by a parenteral route.

Many important drugs are available only as parenteral dosage forms. Notable among these are biotechnology drugs; insulin; several cephalosporin antibiotic products; and drugs such as heparin, protamine, and glucagon. In addition, other drugs, such as lidocaine hydrochloride and many anticancer products, are used principally as parenterals. The reasons that certain drugs are administered largely or exclusively by the parenteral route are very inefficient or unreliable absorption from the GIT, destruction or inactivation in the GIT, extensive mucosal or first-pass metabolism following oral administration, or clinical need in particular medical situations for rapid, assured high blood and tissue levels.

Along with this astounding growth in the use of parenteral medications, the hospital pharmacist has become a very knowledgeable, key individual in most hospitals, having responsibility for hospital-wide IV admixture programs, parenteral unit-dose packaging, and often central surgical supply. By choice, by expertise, and by responsibility, the pharmacist has accumulated the greatest fund of information about parenteral drugs—not only their clinical use, but also their stability, incompatibilities, methods of handling and admixture, and proper packaging. More and more, nurses and physicians are looking to the pharmacist for guidance on parenteral products.

To support the institutional pharmacist in preparing IV admixtures (which typically involves adding one or more drugs to large-volume parenteral fluids), equipment manufacturers have designed laminar flow units, electromechanical compounding units, transfer devices, and filters specifically adaptable to a variety of hospital programs.

The nurse and physician have certainly not been forgotten either. A wide spectrum of IV and IM administration devices and aids have been made available in recent years for bedside use. Many innovative practitioners have made suggestions to industry that have resulted in product or technique improvements, particularly in IV therapy. The use of parenteral products is growing at a very significant rate in nonhospital settings, such as outpatient surgical centers and homes. The reduction in costs associated with outpatient and home care therapy, coupled with advances in drugs, dosage forms, and delivery systems, has caused a major change in the administration of parenteral products [2].

II. ROUTES OF PARENTERAL ADMINISTRATION

The routes of parenteral administration of drugs are (a) subcutaneous, (b) intramuscular, and (c) intravenous; other more specialized routes are (d) intrathecal, (e) intracisternal, (f) intra-arterial, (g) intraspinal, (h) intraepidural, and (i) intradermal. The intradermal route is not typically used to achieve systemic drug effects. The similarities and differences of the routes or their definitions are highlighted in Table 1. The major routes will be discussed separately.

A. The Subcutaneous Route

Lying immediately under the skin is a layer of fat, the superficial fascia (see Fig. 1 in Chapter 8), that lends itself to safe administration of a great variety of drugs, including vaccines, insulin, scopolamine, and epinephrine. Subcutaneous (SC; also SQ or sub-Q) injections are usually administered in volumes up to 2 ml using a ½- to 1-in. 22-gauge (or smaller) needle. Care must be taken to ensure that the needle is not in a vein. This is done by lightly pulling back on the syringe plunger (aspiration) before making the injection. If the needle is inadvertently located in a vein, blood will appear in the syringe and the injection should not be made. The injection site may be massaged after injection to facilitate drug absorption. Drugs given by this

SUN EXHIBIT 1070, IPR2024-00107, PAGE 8

Table 1 Various Parenteral Routes of Drug Administration

Routes	Usual volume (ml)	Needle commonly used	Formulation constraints	Types of medication administered
Primary parenteral routes				
Small-volume parenterals				
Subcutaneous	2	⅝ in., 23 gauge	Need not be isotonic	Insulin, vaccines
Intramuscular	2	1½ in., 22 gauge	Can be solutions, emulsions, oils, or suspensions, isotonic preferably	Nearly all drug classes
Intravenous	50	Veinpuncture 1½ in., 22 gauge	Solutions and some emulsions	Nearly all drug classes
Large-volume parenterals	100 and larger (infusion unit)	Venoclysis 1½ in., 19 gauge	Solutions and some emulsions	Nearly all drug classes (see precautionary notes in text)
Other parenteral routes				
Intra-arterial: directly into an artery (immediate action sought in peripheral area)	2–20	20–22 gauge	Solutions and some emulsions	Radiopaque media, antineoplastics, antibiotics
Intrathecal (intraspinal; into spinal canal)	1–4	24–28 gauge	Must be isotonic	Local anesthetics, analgesics; neurolytic agents
Intraepidural (into epidural space near spinal column)	6–30	5 in., 16–18 gauge	Must be isotonic	Local anesthetics, narcotics, α_2-agonists, steroids
Intracisternal: directly into caudal region of the brain between the cerebellum and the medulla oblongata			Must be isotonic	
Intra-articular: directly into a joint, usually for a local effect there, as for steroid anti-inflammatory action in arthritis	2–20	1.5–2 in., 18–22 gauge	Must be isotonic	Morphine, local anesthetics, steroids, NSAIDs, antibiotics
Intracardial: directly into the heart when life is threatened (epinephrine stimulation in severe heart attack)	0.2–1	5 in., 22 gauge		Cardiotonic drugs, calcium
Intrapleural: directly into the pleural cavity or a lung (also used for fluid withdrawal)	2–30	2–5 in., 16–22 gauge		Local anesthetics, narcotics, chemotherapeutic agents
Diagnostic testing				
Intradermal	10	⅝ in., 26 gauge	Should be isotonic	Diagnostic agents

route will have a slower onset of action than by the IM or IV routes, and total absorption may also be less.

Sometimes dextrose or electrolyte solutions are given subcutaneously in amounts from 250 to 1000 ml. This technique, called hypodermoclysis, is used when veins are unavailable or difficult to use for further medication. Irritation of the tissue is a danger with this technique. Administration of the enzyme hyaluronidase can help by increasing absorption and decreasing tissue distention. Irritating drugs and vasoconstrictors can lead to abscesses, necrosis, or inflammation when given subcutaneously. Body sites suitable for SC administration include most portions of the arms and legs plus the abdomen. When daily or frequent administration is required, the injection site can and should be continuously changed or rotated, especially by diabetic patients self-administering insulin.

B. The Intramuscular Route

The IM route of administration is second only to the IV route in rapidity of onset of systemic action. Injections are made into the striated muscle fibers that lie beneath the subcutaneous layer. The principal sites of injection are the gluteal (buttocks), deltoid (upper arm), and vastus lateralis (lateral thigh) muscles. The usual volumes injected range from 1.0 to 3.0 ml, with volumes up to 10.0 ml sometimes being given (in divided doses) in the gluteal or thigh areas (see Table 1). Again, it is important to aspirate before injecting to ensure that the drug will not be administered intravenously. Needles used in administering IM injections range from 1 to 1½ in. and 19 to 22 gauge, the most common being 1½ in. and 22 gauge.

The major clinical problem arising from IM injections is muscle or neural damage, the injury normally resulting from faulty technique, rather than the medication.

Most injectable products can be given intramuscularly. As a result, there are numerous dosage forms available for this route of administration: solutions, oil-in-water (o/w) or water-in-oil (w/o) emulsions, suspensions (aqueous or oily base), colloidal suspensions, and reconstitutable powders. Those product forms in which the drug is not fully dissolved generally result in slower, more gradual drug absorption, a slower onset of action, and sometimes longer-lasting drug effects.

Intramuscularly administered products typically form a "depot" in the muscle mass from which the drug is slowly absorbed. The peak drug concentration is usually seen within 1–2 hr. Factors affecting the drug-release rate from an IM depot include the compactness of the depot (the less compact and more diffuse, the faster the release), the rheology of the product (affects compactness), concentration and particle size of drug in the vehicle, nature of the solvent or vehicle, volume of the injection, tonicity of the product, and physical form of the product.

C. The Intravenous Route

Intravenous medication is injected directly into a vein either to obtain an extremely rapid and predictable response or to avoid irritation of other tissues. This route of administration also provides maximum availability and assurance in delivering the drug to the site of action. However, a major danger of this route of administration is that the rapidity of absorption makes antidoting very difficult, if not impossible, in most instances. Care must also be used to avoid too rapid a drug administration by the IV route because irritation or an excessive drug concentration at the target organ (drug shock) can occur. The duration of drug activity is dependent on the initial dose and the distribution, metabolism, and excretion properties (pharmacokinetics) of the drug. For most drugs, the biological half-life is independent of the initial dose, because the elimination process is first-order. Thus, an intravenous drug with a short half-life would not

SUN EXHIBIT 1070, IPR2024-00107, PAGE 10

provide a sustained blood level. The usual method of administration for drugs with short half-lives is to use continuous IV drip. Intravenous injections (vein puncture) normally range from 1 to 100 ml and are given with either a 20- or 22-gauge 1½-in. needle, with an injection rate of 1 ml/10 sec for volumes up to 5 ml and 1 ml/20 sec for volumes over 5 ml. Only drugs in aqueous or hydroalcoholic solutions are to be given by the IV route.

Large proximal veins, such as those located inside the forearm, are most commonly used for IV administration. Because of the rapid dilution in the circulating blood and the general insensitivity of the venous wall to pain, the IV route may be used to administer drugs that would be too irritating or caustic to give by other routes (e.g., nitrogen mustards), provided that proper dosing procedures are employed. The risk of thrombosis is increased when extremity sites such as the wrist or ankle are used for injection sites, or when potentially irritating IV products are used, with the risk further increasing in patients with impaired circulation.

The IV infusion of large volumes of fluids (100–1000 ml) has become increasingly popular (Figs. 1 and 2). This technique, called *venoclysis*, utilizes products known as large-volume parenterals (LVPs). It is used to supply electrolytes and nutrients, to restore blood volume, to prevent tissue dehydration, and to dilute toxic materials already present in body fluids. Various parenteral drug solutions may often be conveniently added to the LVP products as they are being administered (Figs. 3 and 4), or before administration, to provide continuous and prolonged drug therapy. Such drug additions to LVP has become very common in hospitals. Combining parenteral dosage forms for administration as a unit product is known as *IV admixtures*. Pharmacists practicing such IV additive product preparation must be very knowledgeable to avoid physical and chemical incompatibilities in the modified LVP, creation of any therapeutic incompatibilities with other drugs being given parenterally or by any other route, or loss of sterility or addition of extraneous matter.

Commonly administered large-volume parenterals include such products as sodium chloride injection [USP] (0.9% saline), which replenish fluids and electrolytes, and 5% dextrose injection [USP], which provides fluid plus nutrition (calories) or various combinations of dextrose and saline. In addition, numerous other nutrient and ionic solutions are available for clinical use, the most popular of which are solutions of essential amino acids or lipid emulsions. These solutions are modified to be hypertonic, isotonic, or hypotonic to aid in maintaining both fluid, nutritional, and electrolyte balance in a particular patient according to need. Indwelling needles or catheters are required in LVP administration. Care must be taken to avoid local or systemic infections or thrombophlebitis owing to faulty injection or administration technique.

D. Other Parenteral Routes

Other more specialized parenteral routes are listed and described briefly in Table 1. The intra-arterial route involves injecting a drug directly into an artery. This technique is not simple and may require a surgical procedure to reach the artery. It is important that the artery not be missed, since serious nerve damage can occur to the nerves lying close to arteries. Doses given by this route should be minimal and given gradually, since, once injected, the drug effect cannot be neutralized. As shown in Table 1, the intra-arterial route is used to administer radiopaque contrast media for viewing an organ, such as the heart or kidney, or to perfuse an antineoplastic agent at the highest possible concentration to the target organ.

The intrathecal route is employed to administer a drug directly into the cerebrospinal fluid at any level of the cerebrospinal axis. This route is used when it is not possible to achieve sufficiently high plasma levels to accomplish adequate diffusion and penetration into the cerebrospinal fluid. This is not the same route used to achieve spinal anesthesia, for which the drug is injected within the dural membrane surrounding the spinal cord, or in extradural or

SUN EXHIBIT 1070, IPR2024-00107, PAGE 11

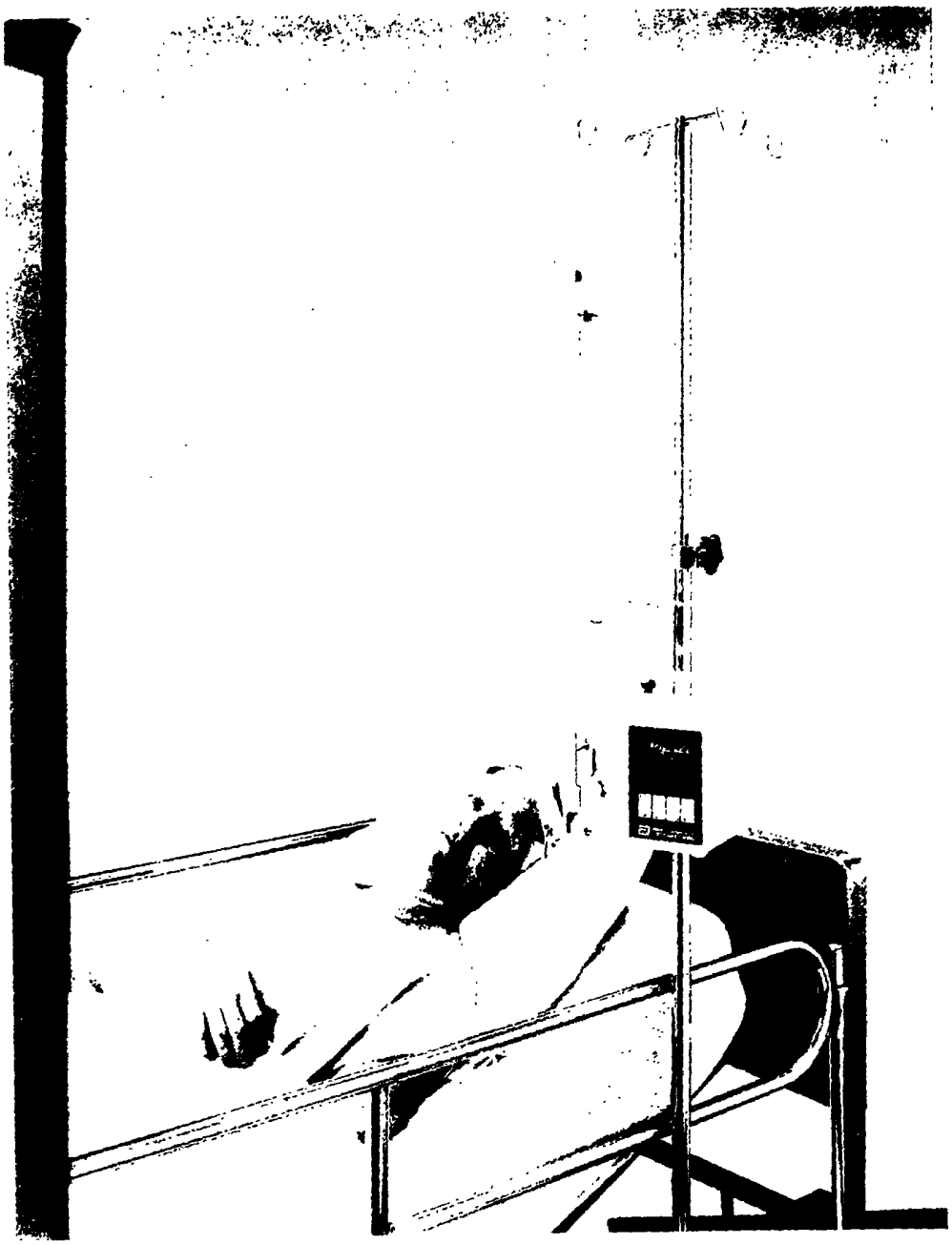

Fig. 1 Administration of an intravenous fluid by electronic flow control.

Fig. 2 Direct intravenous administration using gum rubber injection site.

epidural anesthesia (caudal or sacral anesthesia), for which the drug is deposited outside the dural membrane and within the body spinal caudal canals. Parenteral products administered by the intrathecal, intraspinal, and intracisternal routes must be especially carefully formulated, with ingredients of the highest purity because of the sensitivity of nerve tissue.

Intradermal (ID) administration involves injection into the skin layer (see Fig. 3 in Chapter 8). Examples of drugs administered by this route are allergy test materials. Since intradermal drugs are normally given for diagnostic purposes, it is important that the product per se be nonirritating. Volumes are normally given at 0.05 ml/dose and the solutions are isotonic. Intradermal medication is usually administered with a ½- or ⅝-in., 25- or 26-gauge needle, inserted at an angle nearly parallel to the skin surface. Absorption is slow and limited from this site, since the blood vessels are extremely small, although the area is highly vascular. The site should not be massaged after the injection of allergy test materials. Skin testing includes not only allergens, such as pollens or dust, but also microorganisms, as in the tuberculin or histoplasmin skin tests.

III. SPECIALIZED LARGE-VOLUME PARENTERAL AND STERILE SOLUTIONS

Large-volume parenterals designed to provide fluid (water), calories (glucose solutions), electrolytes (saline solutions), or combinations of these materials have been described. Several other specialized LVP and sterile solutions are also used in medicine and will be described

Fig. 3 Addition of intravenous medication directly to primary intravenous solution container.

here, even though two product classes (peritoneal dialysis and irrigating solutions) are not parenteral products.

A. Hyperalimentation Solutions

Parenteral hyperalimentation involves administration of large amounts of nutrients (e.g., carbohydrates, amino acids, and vitamins) to maintain a patient who is unable to take food orally, for several weeks, at caloric intake levels of 4000 cal/day or more. Earlier methods of parenteral alimentation, which involved IV administration, were not typically able to maintain patients without a weight loss and gradual deterioration in physical condition. Parenteral hyperalimentation involves continuous administration of the nutrient solution into the superior vena cava by an indwelling catheter. Available hyperalimentation solutions vary in various amino acids, vitamins, minerals, and electrolytes. The method permits administration of lifesaving or life-sustaining nutrients to comatose patients or to patients undergoing treatment for esophageal obstruction, GI diseases (including cancer), ulcerative colitis, and other disease states.

B. Peritoneal Dialysis Solutions

The sterile peritoneal dialysis solutions are infused continuously into the abdominal cavity, bathing the peritoneum (the semipermeable membrane covering the viscera of the abdominal cavity), and are then continuously withdrawn. The purpose of peritoneal dialysis is to remove toxic substances from the body, or to aid and accelerate the excretion function normal to the kidneys. The process is employed to counteract some forms of drug or chemical toxicity as

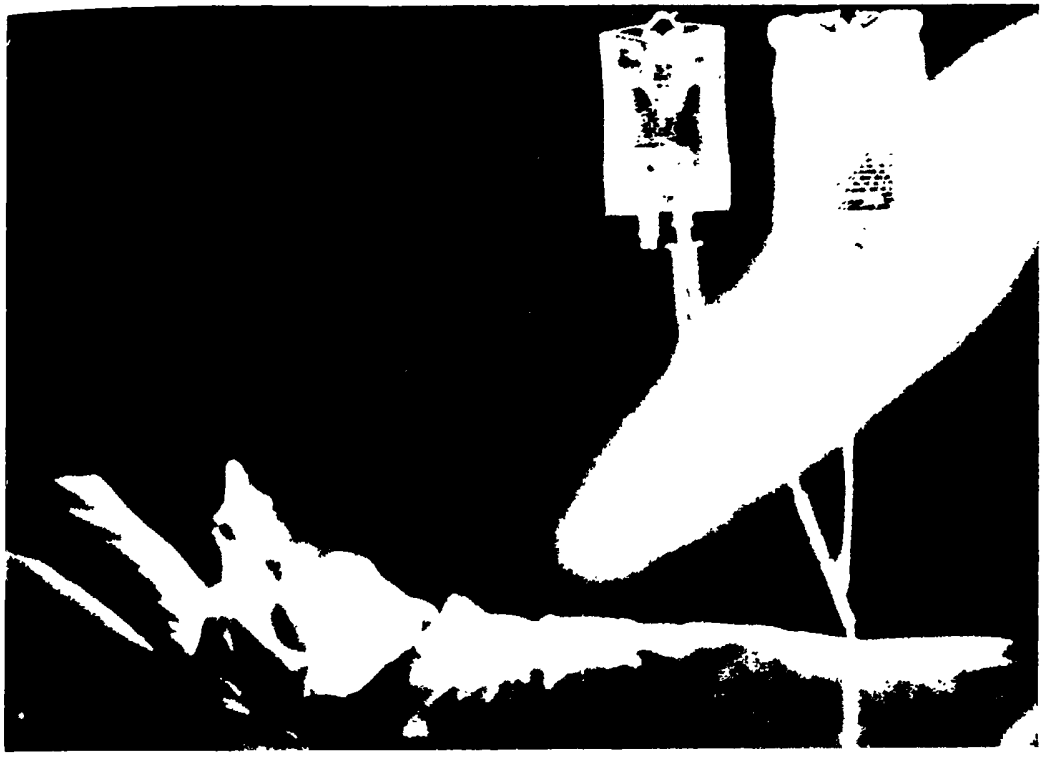

Fig. 4 "Piggybacking" of a small-volume intravenous fluid into the primary large-volume intravenous solution.

well as to treat acute renal insufficiency. Peritoneal dialysis solutions contain glucose and have an ionic content similar to normal extracellular fluid. Toxins or metabolites diffuse into the circulating dialysis fluid through the peritoneum and are removed. At the same time, excess fluid is removed from the patient if the glucose content renders the dialysis solution hyperosmotic. An antibiotic is often added to these solutions as a prophylactic measure.

C. Irrigating Solutions

Irrigating solutions are intended to irrigate, flush, and aid in cleansing body cavities and wounds. Although certain IV solutions, such as normal saline, may be used as irrigating solutions, solutions designed as irrigating solutions should not be used parenterally. Since irrigating solutions used in treatment of serious wounds infuse into the bloodstream to some degree, they must be sterile, pyrogen-free, and made and handled with the same care as parenteral solutions.

IV. PHYSICOCHEMICAL FACTORS AND COMPONENTS

Physicochemical properties of the active drug and the components used in a parenteral dosage form can significantly affect the availability of the drug substance. Other factors that influence drug availability are physiological (biological conditions and disease state of the patient), the route of administration, and the type of dosage form. Intramuscular and subcutaneous routes

of parenteral administration require drug absorption before blood or cerebrospinal fluid levels can be achieved. The rate at which the drug is absorbed has a significant influence on the concentration of the drug in the blood. With an IM suspension, drug dissolution is usually the rate-limiting step in the absorption of the drug at the injection site [3]. The absorption of the drug following IM administration is greatly influenced by the physicochemical properties of the drug.

Components that are incorporated into parenteral dosage forms may have very rigid specifications and standards. Because of these requirements, extensive analytical and toxicological testing is performed to ensure that a chemical is acceptable. Thorough toxicity testing is required of a new drug or other component not previously approved for parenteral use, and the accumulated data are evaluated. Testing may be done on the individual components as well as the final dosage forms. Given such explicit qualities as purity, safety, and lack of (or minimum) pharmacological effect required of parenteral additives, the formulator is restricted to a very few materials as excipients, preservatives, suspending agents, and surfactants. Because of the very extensive pharmacological and toxicological data required to obtain approval for any new additive, most formulators continue to depend on materials of known acceptability.

A. The Active Drug

A thorough evaluation of properties of the active drug or drugs is essential in developing a stable and safe parenteral dosage form. The physical and chemical factors that may significantly affect the development of a parenteral dosage form are discussed in Chapter 7 and by Motola and Agharkar [4]. Important properties include solubility and rate of solution. Factors that influence solubility include particle size; salt, ester, or other chemical form; solution pH; polymorphism; purity; and hydrate formulation.

Crystal Characteristics

Control of the crystallization process to obtain a consistent and uniform crystal form, habit, density, and size distribution is particularly critical for drug substances to be utilized in suspensions or powders. For example, when the crystallization of sterile ceftazidime pentahydrate was modified to significantly increase the density to reduce the volume of the fill dose, the rate of dissolution increased significantly. Many dry solid parenteral products, such as the cephalosporins, are prepared by sterile crystallization techniques.

To obtain a uniform product from lot to lot, strict adherence to the procedures developed for a particular crystallization must be followed, including control of pH, rates of addition, solvent concentrations and purity, temperature, and mixing rates. Each crystallization procedure has to be designed to ensure sterility and minimize particulate contamination. Changes, such as using absolute ethyl alcohol instead of 95% ethanol during the washing procedure, can destroy the crystalline structure if the material being crystallized is a hydrate structure.

Drugs that associate with water to produce crystalline forms are called hydrates. Water content of the hydrate forms of sodium cefazolin as a function of relative humidity is seen in Fig. 5. As shown in Fig. 5, the sesquihydrate is the most stable structure when exposed to extreme humidity conditions [5]. This figure also reveals the importance of choosing the proper combination of hydrate and humidity conditions when designing a manufacturing process or facility.

Chemical Modifications

Improvement of the properties of a drug may be achieved by the chemical modification of the parent drug. The preparation of an ester, salt, or employed other modification of the parent structure may be employed with parenteral drugs to increase stability, alter drug solubility,

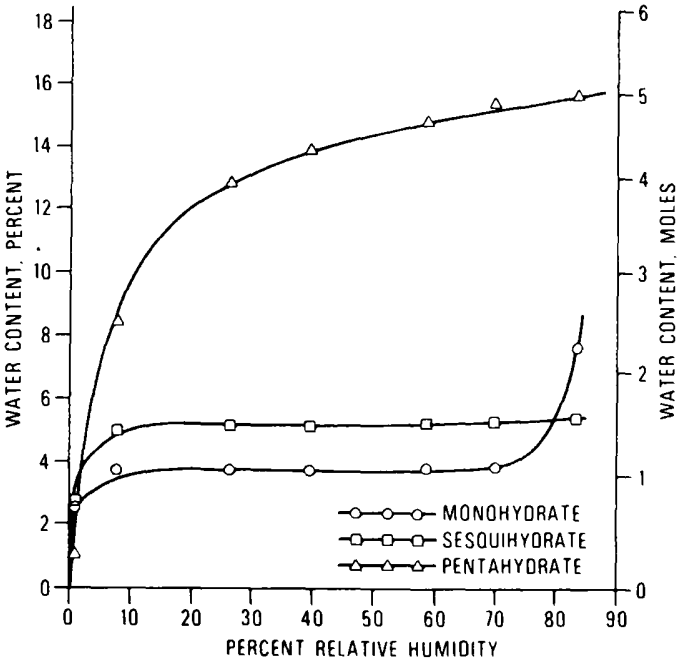

Fig. 5 Relative humidity versus water content of hydrate forms of sodium cefazolin. (From Ref. 5.)

enhance depot action, ease formulation difficulties, and possibly, decrease pain on injection. The molecularly modified drug that converts back to the active parent structure is defined as a *prodrug*. This conversion usually occurs within the body system or, for some drugs that are formulated as dry powders, occurs on reconstitution. The preparation of prodrugs is becoming a common practice with many types of drugs. Examples of antibiotic prodrugs include benzathine penicillin, procaine penicillin, metronidazole phosphate, and chloramphenicol sodium succinate.

The preparation of salts of organic compounds is one of the most important tools available to the formulator. Compounds for both IM and IV solutions require high solubility so that the drug may be incorporated into small volumes for IM administration and also be acceptable for IV use. Sodium and potassium salts of weak acids and hydrochloride and sulfate salts of weak bases are widely used in parenterals requiring highly soluble compounds, based on their overall safety and history of clinical acceptance.

If a drug's solubility is to be reduced to enhance stability or to prepare a suspension, the formulator may prepare water-insoluble salts. A classic example is procaine penicillin G, the decreased solubility (7 mg/ml) of which, when compared with the very soluble penicillin G potassium, is utilized to prepare stable parenteral suspensions. Another alternative to preparing an insoluble drug is to use the parent acidic or basic drug and to buffer the pH of the suspension in the range of minimum solubility.

Polymorphism

The literature lists numerous examples of polymorphism; that is, the existence of several crystal forms of a given chemical that exhibit different physical properties [6]. The conversion of one polymorph to another may cause a significant change in the physical properties of the drug.

Studies of polymorphs in recent years have pointed out the effects of polymorphism on solubility and, more specifically, on dissolution rates. The aspect of polymorphism that is of concern to the parenteral formulator is basically one of product stability [7]. Substances that form polymorphs must be evaluated so that the form used is stable in that particular solvent system. Physical stresses that occur during suspension manufacture may also give rise to changes in crystal form [8].

pH and pK_a

Profiles of pH versus solubility and pH versus stability are needed for solution and suspension formulations to help assure physical and chemical stability as well as to maximize or minimize solubility. This information is also valuable for predicting the compatability of drugs with various infusion fluids.

In summary, the physical and chemical data that should be obtained on the drug substance include the following:

Molecular structure and weight
Melting point
Thermal profile
Particle size and shape
Hygroscopicity potential
Ionization constant
Light stability
Optical activity
pH solubility profile
pH stability profile
Polymorphism potential
Solvate formation

B. Added Substances in Parenteral Formulations

To provide efficacious, safe, and elegant parenteral dosage forms, added substances must frequently be incorporated into the formula to maintain pharmaceutical stability, control product attributes, ensure sterility, or aid in parenteral administration. These substances include antioxidants, antimicrobial agents, buffers, bulking materials, chelating agents, inert gases, solubilizing agents, protectants, and substances for adjusting toxicity. In parenteral product development work, any additive to a formulation must be justified by a clear purpose and function. In addition, every attempt should be made to choose added substances that are accepted by regulatory agencies throughout the world, since most pharmaceutical development is international in scope.

Some of the added substances most commonly used are listed in Table 2. Pharmacists involved in IV additive programs must be aware of the types of additives that may be present in the products being combined.

Antioxidants

Salts of sulfur dioxide, including bisulfite, metasulfite, and sulfite, are the most common antioxidants used in aqueous parenterals. These antioxidants maintain product stability by being preferentially oxidized and gradually consumed over the shelf life of the product. Irrespective of which salt is added to the solution, the antioxidant moiety depends on the final concentration of the thio compound and the final pH of the formulation [9]. While undergoing oxidation

Table 2 Classes and Examples of Parenteral Additives

Additive class	Examples of parenteral additives	Usual concentration (%)
Antimicrobial	Benzalkonium chloride	0.01
	Benzyl alcohol	1–2
	Chlorobutanol	0.25–0.5
	Metacresol	0.1–0.3
	Butyl *p*-hydroxybenzoate	0.015
	Methyl *p*-hydroxybenzoate	0.1–0.2
	Propyl *p*-hydroxybenzoate	0.2
	Phenol	0.25–0.5
	Thimerosal	0.01
Antioxidants	Ascorbic acid	0.01–0.05
	Cysteine	0.1–0.5
	Monothioglycerol	0.1–1.0
	Sodium bisulfite	0.1–1.0
	Sodium metabisulfite	0.1–1.0
	Tocopherols	0.05–0.5
Buffers	Acetates	1–2
	Citrates	1–5
	Phosphates	0.8–2.0
Bulking agents	Lactose	1–8
	Mannitol	1–10
	Sorbitol	1–10
	Glycine	1–2
Chelating agents	Salts of ethylenediaminetetraacetic acid (EDTA)	0.01–0.05
Protectants	Sucrose	2–5
	Lactose	2–5
	Maltose	2–5
	Human serum albumin	0.5–2
Solubilizing agents	Ethyl alcohol	1–50
	Glycerin	1–50
	Polyethylene glycol	1–50
	Propylene glycol	1–50
	Lecithin	0.5–2.0
Surfactants	Polyoxyethylene	0.1–0.5
	Sorbitan monooleate	0.05–0.25
Tonicity-adjusting agents	Dextrose	4–5
	Sodium chloride	0.5–0.9

reactions, the sulfites may be converted to sulfate and other species. Sulfites can also react with certain drug molecules (e.g., epinephrine).

Sulfite levels are determined by the reactivity of the drug, the type of container (glass seal versus rubber stopper), single- or multiple-dose use, container headspace, use of inert gas purge, and the expiration dating period to be employed. Upper limits for sulfite levels are specified in most pharmacopeias; for example, the *USP* allows 3.2 mg of sodium bisulfite per millimeter of solution, whereas the French pharmacopeia (*Pharmacopée Française*) allows only 1.6

mg/ml. Allowances on upper limits are made for concentrated drugs that are diluted extensively before use. An oxygen-sensitive product to be used in France might require a smaller container (less headspace) or a glass seal ampoule to maintain product stability because of the reduced bisulfite level.

Sulfites have been reported to precipitate an allergic reaction in some asthmatics. If possible, alternative antioxidants should be considered or the product should be manufactured and packaged in a manner such as to eliminate or minimize the concentration of bisulfite required. Deoxygenation of the makeup water, maintaining the solution under a nitrogen atmosphere throughout the manufacturing process, and purging the filled vials with an inert gas could significantly reduce the amount of antioxidant required.

Antimicrobial Agents

A suitable preservative system is required in all multiple-dose parenteral products to inhibit the growth of microorganisms accidentally introduced during withdrawal of individual doses. Preservatives may be added to single-dose parenteral products that are not terminally sterilized as a sterility assurance measure; that is, to prevent growth of any microorganisms that could be introduced if there were any inadvertent breach of asepsis during filling operations. However, the inclusion of a preservative in single-dose parenteral products must be weighed against the need to develop formulations that are acceptable to regulatory bodies worldwide. Inclusion of a preservative can be a difficult challenge here, given the wide range of viewpoints concerning which preservatives are acceptable and when it is appropriate to include them in a formulation. Partly because of this, there is a trend in parenteral product development to eliminate preservatives wherever it is practical to do so. This may require added measures in manufacturing to improve sterility assurance—such as using barrier technology to provide positive separation of personnel from product during aseptic filling and transfer steps.

The formulation scientist must be aware of interactions between preservatives and other components of a formulation that could compromise the efficacy of the preservative. For example, proteins can bind thimerosal, reducing preservative efficacy. Partitioning of preservative into a micellar phase or an oil phase (in an emulsion) can also reduce the effective concentration of preservative available for bactericidal or bacteriostatic action. Preservative efficacy testing should be done on the proposed formulation to assure an effective preservative concentration.

Several investigators have published research on incompatibilities of preservatives with rubber closures and other packaging components, particularly polymeric materials [10]. Again, challenging the product with selected microorganisms to measure bacteriostatic or bactericidal activity is necessary, including evaluation of efficacy as a function of time throughout the anticipated shelf life of the product.

More subtle effects of preservatives on injectable formulations are possible. Formulation of insulin is an illustrative case study. Insulin is usually formulated as a multiple-dose vial, since individual dosage varies among patients. Preservation of zinc insulin with phenol causes physical instability of the suspension, whereas methylparaben does not. However, the presence of phenol is required for obtaining protamine insulin crystals [8].

Buffers

Many drugs require a certain pH range to maintain product stability. As discussed previously, drug solubility may also be strongly dependent on the pH of the solution. An important aid to the formulator is the information contained in a graph of the solubility profile of the drug as a function of pH (Fig. 6). The product can then be buffered to approach maximum or minimum solubility, whichever is desired.

Parenteral products should be formulated to possess sufficient buffer capacity to maintain proper product pH. Factors that influence pH include product degradation, container and stopper

SUN EXHIBIT 1070, IPR2024-00107, PAGE 20

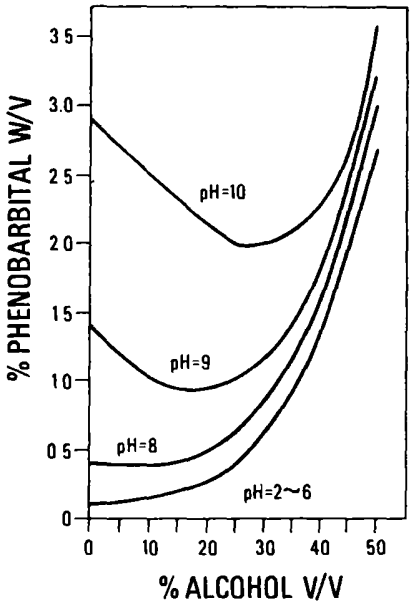

Fig. 6 Interdependence of pH and alcohol concentration on the solubility of phenobarbital. (From Ref. 11.)

effects, diffusion of gases through the closure, and the effect of gases in the product or in the headspace. However, the buffer capacity of a formulation must be readily overcome by the biological fluids; thus, the concentration and ratios of buffer ingredients must be carefully selected.

Buffer systems for parenterals consist of either a weak base and the salt of a weak base or a weak acid and the salt of a weak acid. Buffer systems commonly used for injectable products are acetates, citrates, and phosphates (see Table 2). Amino acids are receiving increased use as buffers, especially for polypeptide injectables.

Chelating Agents

Chelating agents are added to complex and, thereby, inactivate metals such as copper, iron, and zinc that generally catalyze oxidative degradation of drug molecules. Sources of metal contamination include raw material impurities; solvents, such as water, rubber stoppers and containers; and equipment employed in the manufacturing process [12]. The most widely used chelating agents are ethylenediaminetetraacetic acid (edetic acid; EDTA) derivatives and salts. Japan does not allow the use of these particular chelating agents in any parenteral products. Citric and tartaric acids are also employed as chelating agents.

Inert Gases

Another means of enhancing the product integrity of oxygen-sensitive medicaments is by displacing the air in the solution with nitrogen or argon. This technique may be made more effective by first purging with nitrogen or boiling the water to reduce dissolved oxygen. The container is also purged with nitrogen or argon before filling and may also be topped off with the gas before sealing.

SUN EXHIBIT 1070, IPR2024-00107, PAGE 21

Glass-seal ampoules provide the most impervious barrier for gas transmission. A butyl rubber stock is used with rubber-stoppered products that are sensitive to oxygen because it provides better resistance to gas permeation than other rubber stocks.

Solubilizing Agents and Surfactants

Drug solubility can be increased by the use of solubilizing agents, such as those listed in Table 2, and by nonaqueous solvents or mixed solvent systems, to be discussed shortly. When using solubilizing agents, the formulator must consider their effect on the safety and stability of the drug.

A surfactant is a surface-active agent that is used to disperse a water-insoluble drug as a colloidal dispersion. Surfactants are used for wetting and to prevent crystal growth in a suspension. Surfactants are used quite extensively in parenteral suspensions for wetting powders and to provide acceptable syringability. They are also used in emulsions and for solubilizing steroids and fat-soluble vitamins.

Tonicity Adjustment Agents

It is important that injectable solutions that are to be given intravenously are isotonic, or nearly so. Because of osmotic pressure changes and the resultant exchange of ionic species across red blood cell membranes, nonisotonic solutions, particularly if given in quantities larger than 100 ml, can cause hemolysis or crenation of red blood cells (owing to hypotonic or hypertonic solutions, respectively). Dextrose and sodium chloride or potassium chloride are commonly used to achieve isotonicity in a parenteral formula.

Protectants

A protectant is a substance that is added to a formulation to protect against loss of activity caused by some stress that is introduced by the manufacturing process or to prevent loss of active ingredients by adsorption to process equipment or to primary packaging materials. Protectants are used primarily in protein and liposomal formulations. For example, cryoprotectants and lyoprotectants are used to inhibit loss of integrity of the active substance resulting from freezing and drying, respectively. Compounds that provide cryoprotection are not necessarily the same as those that provide lyoprotection. For example, polyethylene glycol protects lactate dehydrogenase and phosphofructokinase from damage by freezing, but does not protect either protein from damage by freeze-drying. Compounds such as glucose and trehalose are effective lyoprotectants for both proteins [13]. Effective cryo- and lyoprotectants must be determined on a case-by-case basis, but sugars and polyhydroxy compounds are usually the best candidate compounds. These same types of compounds also tend to markedly improve the stability of proteins against inactivation by thermal denaturation.

Another type of protectant is used to prevent loss of active substance—again, usually a protein and usually present at a very low concentration—by adsorption to materials or equipment in the manufacturing process or to components of the primary package. In manufacturing, particular attention should be given to adsorption of the active entity to filters (especially nylon) and to silicone tubing used for transfer operations. For packaging materials, rubber closures and other polymeric materials should be examined carefully for adsorptive potential. The same consideration applies to infusion equipment, particularly considering that most materials in modern IV infusion therapy are polymeric.

Human serum albumin (HSA) is commonly used as a protectant against adsorptive loss. HSA is present at higher concentration than the active substance, and is preferentially adsorbed, coating the surface of interest and preventing adsorption of the drug. For example, insulin is subject to adsorptive loss to hydrophobic materials. Addition of 0.1–1.0% HSA has been reported to prevent adsorptive loss [8].

SUN EXHIBIT 1070, IPR2024-00107, PAGE 22

C. Vehicles

Aqueous Vehicles

"Water for injection" (WFI) is the most widely used solvent for parenteral preparations. The requirements for WFI are generally the same throughout the world. Companies involved in international markets must be assured that their products comply with the applicable standards. The most common means of obtaining WFI is by the distillation of deionized water. Water for injection must be prepared and stored in a manner to ensure purity and freedom from pyrogens.

Microorganisms, dissolved organic and inorganic substances, and foreign particles are the most common contaminants found in water. New purification methods and systems are continually being investigated to improve the quality of water for parenteral use. Inorganic compounds are commonly removed by distillation, reverse osmosis, deionization, or a combination of these processes. Membrane and depth filters are used to remove particulate contaminants, and charcoal beds may be used to remove organic materials. Filtration, chilling or heating, or recirculation of water are used to reduce microbial growth and to prevent pyrogen formation that will occur in a static deionization system. To inhibit microbial growth, WFI must be stored at either 5°C or 60–90°C if it is to be held for over 24 hr.

The *USP* also lists sterile water for injection and bacteriostatic water for injection, which unlike WFI, must be sterile. Higher levels of solids are allowed in these vehicles because of the possible leaching of glass constituents into the product during high-temperature sterilization and subsequent storage. Bacteriostatic water for injection must not be placed in containers larger than 30 ml. This is to prevent the administration of large quantities of bacteriostatic agents (such as phenol) that could become toxic if large volumes of solution were administered. Other aqueous vehicles that may be used in place of sterile water for injection or bacteriostatic water for injection for reconstitution or administering drugs include 5% dextrose, 0.9% sodium chloride, and a variety of other electrolyte and nutrient solutions, as noted earlier.

Nonaqueous and Mixed Vehicles

A nonaqueous solvent or a mixed aqueous–nonaqueous solvent system may be necessary to stabilize drugs, such as the barbiturates, that are readily hydrolyzed by water, or to improve solubility (e.g., digotoxin). Nonaqueous solvents must be carefully screened and tested to ensure that they exhibit no pharmacological action, are nontoxic and nonirritating, and are compatible and stable with all ingredients of a formulation.

A major class of nonaqueous solvents is the fixed oils. The *USP* [1] recognizes the use of fixed oils as parenteral vehicles and lists their requirements. The most commonly used oils are corn oil, cottonseed oil, peanut oil, and sesame oil. Because fixed oils can be quite irritating when injected and may cause sensitivity reactions in some patients, the oil used in the product must be stated on the label.

Sesame oil is the preferred oil for most of the official injections in oil. This is because it is the most stable (except in light) and, thus, will usually meet the official requirements. Fixed oils must never be administered intravenously and are, in fact, restricted to IM use.

The *USP* usually does not specify an oil, but states that a suitable vegetable oil can be used. The main use of such oils is with the steroids, with which they yield products that produce a sustained-release effect. Sesame oil has also been used to obtain slow release of fluphenazine esters given intramuscularly [4]. Excessive unsaturation of an oil can produce tissue irritation. The use of injections in oil has diminished somewhat in preference to aqueous suspensions,

SUN EXHIBIT 1070, IPR2024-00107, PAGE 23

which generally have less irritating and sensitizing properties. Benzyl benzoate may be used to enhance steroid solubility in oils if desired.

Water-miscible solvents are widely used in parenterals to enhance drug solubility and to serve as stabilizers. The more common solvents include glycerin, ethyl alcohol, propylene glycol, and polyethylene glycol 300. A common example of an injectable product formulated with nonaqueous solvents is IV Valium, which contains 40% propylene glycol and 10% ethanol. Mixed-solvent systems do not exhibit many of the disadvantages observed with the fixed oils, but may also be irritating or increase toxicity, especially when present in large amounts or in high concentrations. A solution containing a high percentage of ethanol will produce pain on injection.

The formulator should be aware of the potential of nonaqueous solvents in preparing a solubilized or stable product that may not have been otherwise possible. The reader is directed to comprehensive reviews of nonaqueous solvents for additional information [15,16].

V. DOSAGE FORMS

A. Solutions

The most common of all injectable products are solutions. Solutions of drugs suitable for parenteral administration are referred to as *injections*. Although usually aqueous, they may be mixtures of water with glycols, alcohol, or other nonaqueous solvents. Many injectable solutions are manufactured by dissolving the drug and a preservative, adjusting the pH, sterile filtering the resultant solution through a 0.22-μm–membrane filter and, when possible, autoclaving the final product. Most solutions have a viscosity and surface tension very similar to water, although streptomycin sulfate injection and ascorbic acid injection, for example, are quite viscous.

Sterile filtration, with subsequent aseptic filling, is common because of the heat sensitivity of most drugs. Those drug solutions that can withstand heat should be terminally autoclave-sterilized after filling, since this better assures product and package sterility.

Large-volume parenterals (LVPs) and small-volume parenterals (SVPs) containing no antimicrobial agent should be terminally sterilized. It is standard practice to include an antimicrobial agent in SVPs that cannot be terminally sterilized or are intended for multiple-dose use. The general exceptions are products that pass the *USP* Antimicrobial Preservative Effectiveness Test [1] because of the preservative effect of the active ingredient, vehicle, pH, or a combination of these. For example, some barbiturate products have a pH of 9–10 and a vehicle that includes glycol and alcohol.

Injections and infusion fluids must be manufactured in a manner that will minimize or eliminate haze and color. Parenteral solutions are generally filtered through 0.22-μm–membrane filters to achieve sterility and remove particulate matter. Prefiltration through a coarser filter is often necessary to maintain adequate flow rates, or to prevent clogging of the filters during large-scale manufacturing. A talc or carbon filtration aid (or other filter aids) may also be necessary. If talc is used, it should be pretreated with a dilute acid solution to remove surface alkali and metals.

The formulator must be aware of the potential for binding when filtering protein solutions. Because of the cost–availability of most protein materials, a membrane should be used that minimizes protein adsorption to the membrane surface. Typical filter media that minimize this binding include hydrophilic polyvinylidene difluoride and hydroxyl-modified hydrophilic polyamide membranes [17]. Filter suppliers will evaluate the compatibility of the drug product with their membrane media and also validate the selected membrane.

SUN EXHIBIT 1070, IPR2024-00107, PAGE 24

The total fluid volume that must be filled into a unit parenteral container is typically greater than the volume that would contain the exact labeled dose. The fill volume is dependent on the viscosity of the solution and the retention of the solution by the container and stopper. The *USP* [1] provides a procedure for calculating the fill dose that is necessary to ensure the delivery of the stated dose. It also provides a table of excess volumes that are usually sufficient to permit withdrawal and administration of the labeled volume.

B. Suspensions

One of the most difficult parenteral dosage forms to formulate is a suspension. It requires a delicate balance of variables to formulate a product that is easy to fill, ships without caking or settling, and ejects through an 18- to 21-gauge needle through its shelf life. To achieve these properties it is necessary to select and carefully maintain particle size distribution, zeta potential, and rheological parameters, as well as the manufacturing steps that control wettability and surface tension. The requirements for, limitations in, and differences between the design of injectable suspensions and other suspensions have been previously summarized [18,19].

A formula for an injectable suspension might consist of the active ingredient suspended in an aqueous vehicle containing an antimicrobial preservative, a surfactant for wetting, a dispersing or suspending agent, and perhaps a buffer or salt.

Two basic methods are used to prepare parenteral suspensions: (a) sterile vehicle and powder are combined aseptically, or (b) sterile solutions are combined and the crystals formed in situ. Examples of these procedures may be illustrated using sterile penicillin G procaine suspension (*USP*) and sterile testosterone suspension (*USP*).

In the first example, procaine penicillin, an aqueous vehicle containing the soluble components (such as lecithin, sodium citrate, povidone, and polyoxyethylene sorbitan monooleate) is filtered through a 0.22-μm–membrane filter, heat sterilized, and transferred into a presterilized mixing–filling tank. The sterile antibiotic powder, which has previously been produced by freeze-drying, sterile crystallization, or spray-drying, is gradually added to the sterile solution aseptically while mixing. After all tests have been completed on the bulk material, it is aseptically filled.

An example of the second method of parenteral suspension preparation is testosterone suspension. Here, the vehicle is prepared and sterile-filtered. The testosterone is dissolved separately in acetone and sterile-filtered. The testosterone–acetone solution is aseptically added to the sterile vehicle, causing the testosterone to crystallize. The resulting suspension is then diluted with sterile vehicle, mixed, the crystals allowed to settle, and the supernatant solution siphoned off. This procedure is repeated several times until all the acetone has been removed. The suspension is then brought to volume and filled in the normal manner.

The critical nature of the flow properties of parenteral suspensions becomes apparent when one remembers that these products are frequently administered through 1¼-in. or longer needles having internal diameters in the range of only 300–600 μm. In addition, microscopic examination shows a very rough interior needle surface, further hindering flow. The flow properties of parenteral suspensions are usually characterized on the basis of syringeability or injectability. The term *syringeability* refers to the handling characteristics of a suspension while drawing it into and manipulating it in a syringe. Syringeability includes characteristics such as ease of withdrawal from the container into the syringe, clogging and foaming tendencies, and accuracy of dose measurement. The term *injectability* refers to the properties of the suspension during injection; it includes such factors as pressure or force required for injection, evenness of flow, aspiration qualities, and freedom from clogging. The syringeability and injectability characteristics of a suspension are closely related to viscosity and to particle characteristics.

C. Emulsions

An emulsion is a heterogeneous dispersion of one immiscible liquid in another. This inherently unstable system is made possible through the use of an emulsifying agent, which prevents coalescence of the dispersed droplets. Parenteral emulsions are rare because it is necessary (and difficult) to achieve stable droplets of less than 1 μm to prevent emboli in the blood vessels, and it is not usually necessary to achieve an emulsion for drug administration.

Parenteral emulsions have been used for several purposes, including (a) water-in-oil emulsions of allergenic extracts (given subcutaneously), (b) oil-in-water sustained-release depot preparations (given intramuscularly), and (c) oil-in-water nutrient emulsions (given intravenously). Formulation options are severely restricted through a very limited selection of stabilizers and emulsifiers, primarily owing to the dual constraints of autoclave sterilization and parenteral injection. Additionally, unwanted physiological effects (e.g., pyrogenic reaction and hemolysis) have further limited the use of intravenous emulsions.

An increasingly popular class of intravenous emulsions is fat emulsions. These preparations have been available in Europe for over 20 years and in the United States since 1975. Fat is transported in the bloodstream as small droplets called chylomicra. Chylomicra are 0.5- to 1.0-μm spheres consisting of a central core of triglycerides and an outer layer of phospholipids. Intravenous fat emulsions usually contain 10% oil, although they may range up to 20% (Table 3). These emulsions yield triglycerides that provide essential fatty acids and calories during total parenteral nutrition of patients who are unable to absorb nutrients through the gastrointestinal tract. The products commercially available in the United States range from 0.1 to 0.5 μm and have a pH of 5.5–8 (blood plasma has a pH of 7.4). Glycerol and glucose are added to make the product isotonic.

D. Dry Powders

Many drugs are too unstable—either physically or chemically—in an aqueous medium to allow formulation as a solution, suspension, or emulsion. Instead, the drug is formulated as a dry powder that is reconstituted by addition of water before administration. The reconstituted product is usually an aqueous solution; however, occasionally it may be an aqueous suspension (for example, ampicillin trihydrate and spectinomycin hydrochloride are sterile powders that are reconstituted to form a sterile suspension).

Dry powders for reconstitution as an injectable product may be produced by several methods—filling the product into vials as a liquid and freeze-drying, aseptic crystallization followed by powder filling, and spray-drying followed by powder filling. A brief discussion of each follows.

Freeze-Drying

The most common form of sterile powder is a *freeze-dried* or *lyophilized*, powder. The advantages of freeze-drying are that (a) water can be removed at low temperature, avoiding damage to heat-sensitive materials; (b) if freeze-drying is done properly, the dried product has a high specific surface area, which facilitates rapid, complete rehydration (or "reconstitution") of the solid; and (c) from an operations point of view, freeze-dried dosage forms allow drug to be filled into vials as a solution. This makes control of the quantity filled into each vial more precise than filling drug into vials as a powder. In addition, since drug is filled as a solution, there is minimal concern with airborne particulate matter and potential cross-contamination as is the problem with powder filling.

Despite the advantages of freeze-drying, there are some limitations that must be kept in mind.

SUN EXHIBIT 1070, IPR2024-00107, PAGE 26

Table 3 Intravenous Fat Emulsions

Component (g/100 ml)	Intralipid[a]		Liposyn II[b]		Infonutrol[c]	Lipofundin[d]	Lipihysan[e]	
	10%	20%	10%	20%	15%	10%	10%	15%
Soybean oil	10	20	5	10				
Safflower oil			5	10				
Cottonseed oil					15	10	10	15
Egg phospholipids	1.2	1.2	1.2	1.2				
Soybean phospholipids					1.2	1.2		
Soybean lecithin							1.5	2
Glycerol	2.25	2.25	2.5	2.5				
Glucose					4			
Sorbitol						5	5	5
Pluronic F-68					0.3			
DL-α-Tocopherol							0.05	0.05
Water for injections q.s. ad	100 ml	100 ml	100 ml	100 ml	100 ml	100 ml	100 ml	

[a]Kabı-Vitrum A. G., Stockhold, Sweden.
[b]Abbott Laboratories, North Chicago, IL.
[c]Astra-Hewlett, Södertäye, Sweden
[d]Braun. Melsunger, West Germany
[e]Egic, L'Equilibre Biologique S. A., Loiret, France

1. Some proteins are damaged by freezing, freeze-drying, or both. Although the damage can often be minimized by using protective agents in the formulation, the problem is still substantial.
2. Often the stability of a drug in the solid state depends on its physical state (i.e., crystalline or amorphous [20]). If freeze-drying produces an amorphous solid, and the amorphous form is not stable, then freeze-drying will not provide an acceptable product.
3. Freeze-drying is a relatively expensive drying operation. Although this is not an issue for many high-cost drug products, it may become an issue for more cost-sensitive pharmaceutical products.

In freeze-drying, a solution is filled into vials, a special slotted stopper is partially inserted into the neck of the vial (Fig. 7), and trays of filled vials are transferred to the freeze-dryer (Fig. 8). The solution is frozen by circulation of a fluid, such as silicone oil, at a temperature in the range of −35° to about −45°C through internal channels in the shelf assembly. When the product has solidified sufficiently, the pressure in the freeze-dry chamber is reduced to a pressure less that the vapor pressure of ice at the temperature of the product, and heat is applied to the product by increasing the temperature of the circulating fluid. Under these conditions, water is removed by *sublimation* of ice, or a phase change from the solid state directly to the vapor state without the appearance of an intermediate liquid phase. The phase diagram in Fig. 9 illustrates the difference between freeze-drying and conventional drying methods, during which drying takes place by a phase change from the liquid state to the vapor state. Freeze-drying takes place below the triple point of water, at which solid, liquid, and vapor all coexist in equilibrium. As freeze-drying proceeds, a receding boundary can be observed in the vial as the thickness of the frozen layer decreases. This phase is called *primary drying*, during which ice is removed by direct sublimation through open channels created by prior sublimation of ice. After primary drying, additional drying is necessary to remove any water that did not

Fig. 7 Vials typically used for lyophilization showing special slotted stopper.

freeze during the freezing process, but instead remained associated with the solute. This is called *secondary drying* and consists of water removal by diffusion and desorption of water from the partially dried solid phase. The phases of a typical freeze-dry cycle—freezing, primary drying, and secondary drying—are illustrated by means of a plot of shelf temperature, chamber pressure, and product temperature in Fig. 10.

The most important objective in developing a freeze-dried product is to assure that critical quality attributes are met initially and throughout the shelf life of the product. Examples of critical quality attributes are recovery of original chemical or biological activity after reconstitution, rapid and complete dissolution, appropriate residual moisture level, and acceptable cake appearance. In addition, process conditions should be chosen to maximize process efficiency; that is, those conditions that minimize drying time without adversely affecting product quality. The driving force for sublimation is the vapor pressure of ice, and the vapor pressure of ice is highly temperature-dependent as shown below:

Temperature (°C)	Vapor pressure (mm Hg)
−40	0.096
−30	0.286
−20	0.776
−10	1.950
0	4.579

Therefore, freeze-drying should be carried out at the highest allowable product temperature that maintains the appropriate attributes of a freeze-dried product. This temperature depends

Fig. 8 Filled vials being transferred to freeze dryer.

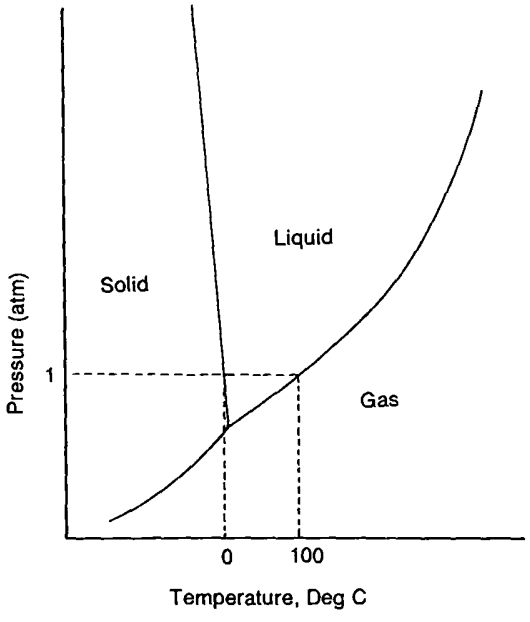

Fig. 9 Phase diagram of water.

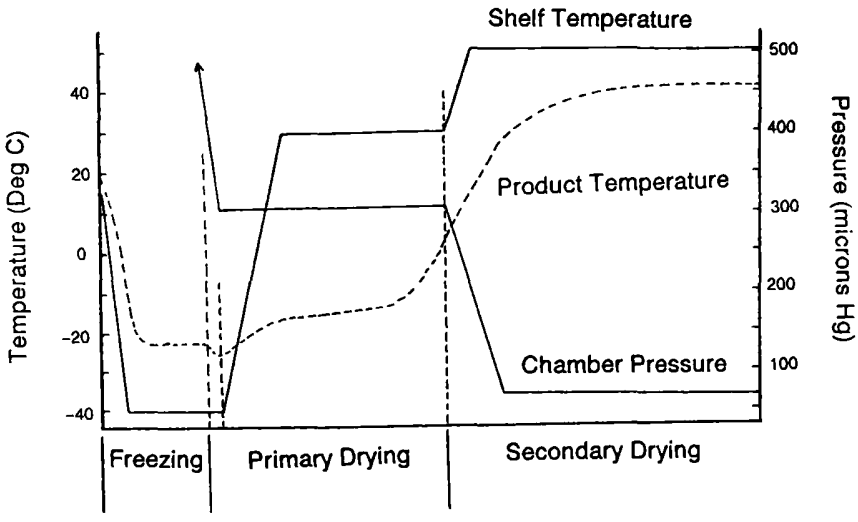

Fig. 10 Process variables during a representative freeze-dry cycle.

on the nature of the formulation. Process development and validation requires characterizing the physical state of the solute, or solutes, that result from the freezing process and identifying a maximum allowable product temperature for the primary drying process [21,22].

The term *eutectic temperature* is often misused in reference to freeze-drying. A eutectic phase—an intimate mixture of ice and crystals of solute that melts as if it were a single, pure compound—is present only if the solute crystallizes when the solution is frozen. Eutectic melting can often be detected by a thermal analysis technique, such as differential scanning calorimetry DSC [23,24]. An example of a eutectic system is neutral glycine in water. The presence of a eutectic phase is indicated by a melting endotherm in the DSC thermogram of the solution (Fig. 11) in addition to the melting endotherm for ice. In this example, the theoretical maximum allowable product temperature during primary drying is the eutectic melting temperature at −3.5°C. In practice, the product temperature should be maintained a few degrees below this temperature to assure that melting does not occur during the process. Examples of some other common solutes that form eutectics, along with the eutectic temperature, are shown below (24):

Solute	Eutectic temperature (°C)
Calcium chloride	−51.0
Citric acid	−12.2
Mannitol	−1.0
Potassium chloride	−10.7
Sodium carbonate	−18.0
Sodium chloride	−21.5
Sodium phosphate, dibasic	−0.5

However, many solutes do not crystallize during the freezing process, but instead, remain amorphous. Examples include sugars, such as sucrose, lactose, maltose, and many polymers. In this case, no eutectic phase is formed. Instead, the freeze concentrate becomes more concentrated and more viscous as the temperature is lowered and ice crystals grow. This process

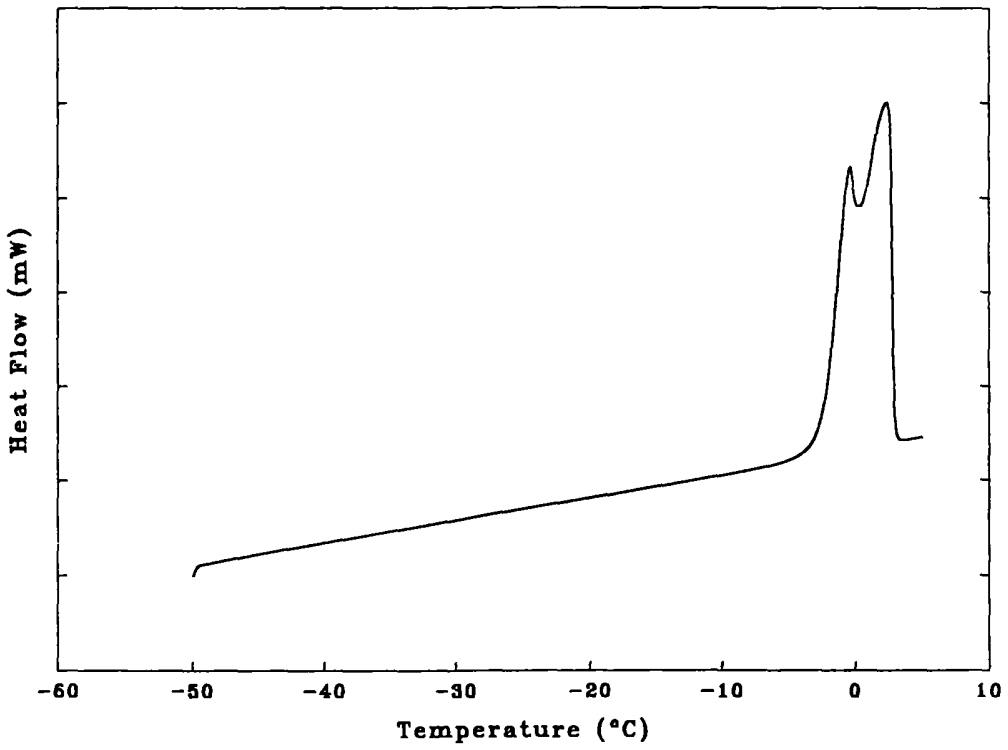

Fig. 11 DSC thermogram of neutral glycine in water.

continues until a temperature is reached at which the viscosity of the freeze concentrate increases dramatically with only a small change in temperature, and ice crystal growth ceases on a practical time scale. This temperature is a *glass transition temperature*, and is an important characteristic of amorphous systems. Below the glass transition temperature, the freeze concentrate exists as a rigid glass. Above the glass transition temperature, the freeze concentrate behaves as a viscous liquid. The significance of the glass transition temperature of the freeze concentrate (commonly referred to as Tg') is that it is closely related to the *collapse temperature* in freeze-drying. If drying is carried out above the collapse temperature, the freeze concentrate will flow and lose the microstructure established by freezing, once the supporting structure of ice crystals is removed. Collapse can be observed in a variety of forms, from a slight shrinkage of the dried cake (where the cake has pulled away from the wall of the vial) to total loss of any cake structure.

The glass transition of solutes that remain amorphous during and after the freezing process can often be seen in the DSC thermogram as a shift in the baseline toward higher heat capacity. This is illustrated in the DSC thermogram of sucrose solution in Fig. 12, in which the glass transition is observed at −34°C. Glass transition (Tg') values of some other solutes common to freeze drying are shown below (24):

Solute	Glass transition (Tg')
Dextran	−9
Gelatin	−10

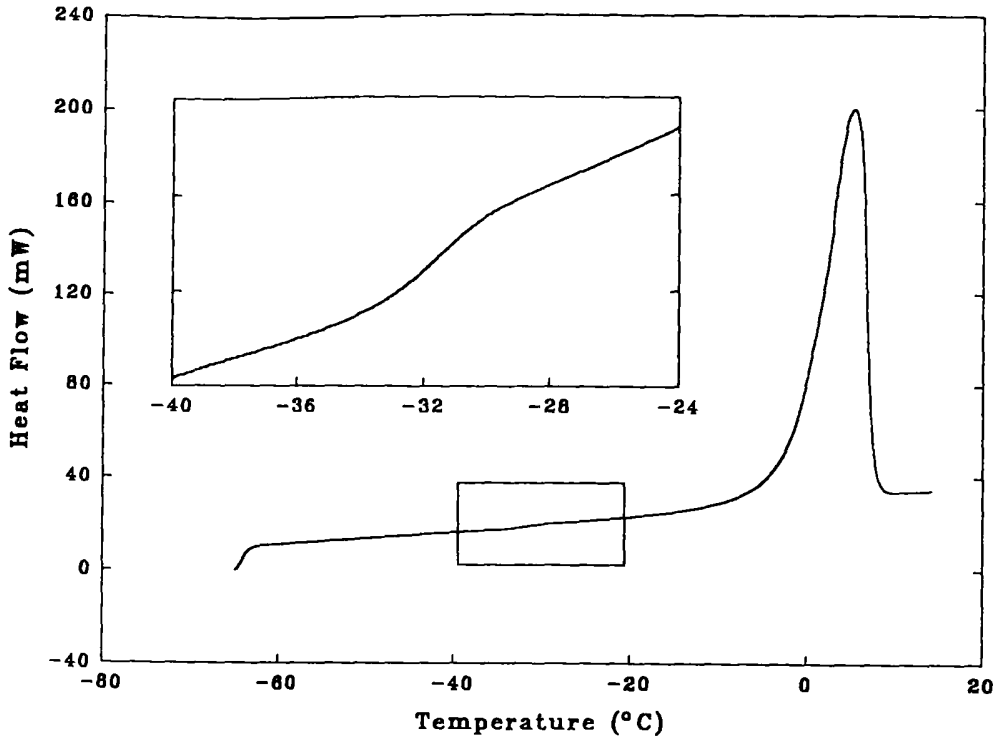

Fig. 12 DSC thermogram of sucrose solution.

Glucose	−43
Lactose	−32
Maltose	−32
Polyvinylpyrrolidone	−24
Sorbitol	−48

Some solutes may first form a metastable amorphous phase initially on freezing and then crystallize when the material is heated. This is the basis for *thermal treatment*, or *annealling*, in the freeze-dry process, during which the product is frozen to perhaps −40°C, the product is then heated to some temperature below the melting point of ice, held for a few hours, then cooled before starting the drying process. Some cephalosporins are known to crystallize by thermal treatment [20], and mannitol is a common excipient which frequently forms a metastable amorphous phase that crystallizes with subsequent heating [26].

In general, crystallization of the solute is desirable in terms of freeze-drying properties, as well as quality attributes of the final product, for several reasons. First, when the solute crystallizes, nearly all of the water is present as ice in the frozen matrix, and it is removed by direct sublimation during primary drying. Therefore, there is little water to be removed by secondary drying. This improves process efficiency, since water removed during secondary drying must be removed primarily by the process of diffusion, rather than by bulk flow. Second, eutectic temperatures are usually higher than collapse temperatures, which allows higher product temperatures and more efficient drying. Eutectic temperatures of most organic compounds are in the range of −1° to about −12°C, whereas collapse temperatures commonly are −30°C

or lower. Third, the chemical and physical stability of a compound in crystalline form is generally better than that of the same compound in an amorphous form [20,27]. This can be a critical aspect of determining the feasibility of a freeze-dried dosage form.

An understanding of the effect of formulation on freeze-drying behavior is important to the pharmaceutical scientist involved in the development of freeze-dried products. Mixtures of components should be expected to behave differently from single-component systems. For example, a compound that crystallizes readily from aqueous solution when it is the only solute present may not crystallize at all when other solutes are present. For solutes that remain amorphous on freezing, the glass transition temperature is affected by the presence of other solutes. Subtle variations in the composition of the formulation, such as changes in ionic strength or pH, may have a significant effect on the physical chemistry of the freezing and freeze-drying processes.

Many drugs are present in a dose too small to form a well-defined freeze-dried cake, and must be formulated with a *bulking agent*, the purpose of which is to provide a dried matrix in which the active ingredient is dispersed. Common bulking agents are mannitol, lactose, glycine, and mixtures of these compounds. Buffers are commonly used, such as sodium or potassium phosphate, acetate, citrate, or tris-hydroxymethylaminomethane (THAM). Formulations of proteins, liposomes, or cells generally require the presence of a *protectant*, or a substance that protects the active compound from damage by freezing, by drying, or both. Disaccharides, such as sucrose, lactose, and maltose, are, in general, the most effective protectants [28]. Trehalose, a disaccharide of glucose, is also a well-known protectant, but is not currently used in freeze-dried products for use in humans.

In addition to the effects of formulation factors on freeze-drying behavior, it is important for the pharmaceutical scientist to understand basic principles of heat and mass transfer in freeze-drying [29,30]. Because of the high heat input required for sublimation—670 calories/g—transfer of heat from the heated shelf to the sublimation front is often the rate-limiting step in the coupled heat and mass transfer process. There are three basic mechanisms for heat transfer: conduction, convection, and radiation. *Conduction* is the transfer of heat by molecular motion between differential volume elements of a material. *Convection* is the transfer of heat by bulk flow of a fluid, either from density differences (natural convection) or because an external force is applied (forced convection). Because of the relatively low pressures used in freeze-drying, convection is probably not a large contributing factor in heat transfer. Heat transfer by *thermal radiation* arises when a substance, because of thermal excitation, emits radiation in an amount determined by its absolute temperature. Of these mechanisms, heat transfer by conduction is the most important. Heat transfer by conduction takes place through a series of resistances—the bottom of the vial, the frozen layer of product, the metal tray (if used), and through the vapor phase caused by lack of good thermal contact between the vial and the shelf. The thermal conductivity of the vapor phase at the pressures used in freeze-drying is dependent on pressure in the chamber. Therefore, to maintain consistent drying conditions from batch to batch, it is as important to control the chamber pressure as it is to control shelf temperature [31]. In addition, changes in the geometry of the system that will affect heat transfer will also affect process consistency. Examples include changing from molded to tubing vials, changing the depth of fill in the vials, and changing from trays with metal bottoms to those without bottoms. Thermal radiation is a small, but significant, contributor to the total quantity of heat transferred to the product. This can be a significant issue in scale-up of cycles from pilot dryers to production-scale equipment.

Mass transfer in freeze-drying refers to the transfer of water vapor from the sublimation front through open channels in the partially dried layer, created by prior sublimation of ice, through the headspace of the vial, past the lyostopper, through the chamber, to the condenser.

The reader is referred to basic studies of mass transfer in freeze-drying by Pikal and co-workers for in-depth treatment of the theoretical and practical aspects of mass transfer [30,32]. Briefly, the rate-limiting step in mass transfer is transfer of water vapor through the partially dried matrix of solids. Resistance of the dried layer increases in a more or less continuous fashion as the depth of the dried layer increases, and the resistance also increases with the concentration of solids in the dried layer. Other factors can also affect the resistance of the dried layer, such as the method of freezing; faster freezing tends to create a higher resistance in the dried layer.

Mass transfer of the "unfrozen" water through a glassy phase during secondary drying occurs slower than bulk flow of water vapor by direct sublimation, since no open channels are present in the glassy phase. The high resistance of the solid material to mass transfer is why secondary drying can be the most time-consuming phase of the freeze-dry cycle for amorphous solutes containing a large percentage of unfrozen water. According to studies reported by Pikal, shelf temperature is the most critical process variable, affecting the rate of secondary drying and final moisture level [32]. Chamber pressure had no measurable influence on secondary drying kinetics.

The quantity of residual water is frequently a critical product characteristic relative to chemical and physical stability of freeze-dried products, particularly amorphous solids. Water acts as a plasticizer of the solid material, lowering the glass transition temperature. A low glass transition temperature, relative to the storage temperature, can result in physical instability, such as cake shrinkage or collapse, or accelerated rates of chemical reactions leading to instability. Often, a small change in moisture content can result in a large change in the glass transition temperature; therefore, careful consideration of appropriate limits on residual moisture is often an important part of the product development process.

Aseptic Crystallization and Dry Powder Filling

Aseptic crystallization is primarily used for manufacture of sterile aqueous suspensions. However, if the physical form of the drug is critical to quality of the final product, better control over physical form can be attained by aseptic crystallization because a large variety of organic solvents can be used to control the crystallization process. In aseptic crystallization, the drug is dissolved in a suitable solvent and sterile filtered through an appropriate membrane filter. A second solvent—a sterilely filtered nonsolvent for the drug—is then added at a controlled rate, causing crystallization and precipitation of the drug. The crystals are collected on a funnel, washed if necessary, and dried by vacuum drying. After drying, it may be necessary to mill or blend the drug crystals. The powder is then transferred to dry–powder-filling equipment and filled into vials. Although simple in principle, there are obvious drawbacks to this approach. Batch-to-batch variability in crystal habit and crystal size and the resulting variability in physical properties can be troublesome for consistent product quality. Maintenance of asepsis between sterile crystallization and filling of the powder is a challenge during material handling, and will usually result in decreased sterility assurance. Also, since the drug is filled into vials as a powder, maintenance of fill weight uniformity is generally more troublesome than when filling with a liquid.

Spray-Drying

A solution of drug is sterile filtered and metered into the drying chamber, where it passes through an atomizer that creates an aerosol of small droplets of liquid (Fig. 13). The aerosol comes into contact with a stream of hot sterile gas—usually air. The solvent evaporates quickly, allowing drug to be collected as a powder in the form of uniform hollow spheres. The powder is then filled into vials using conventional powder-filling equipment. Spray-drying may be more economical than freeze-drying, but challenges in the use of this technique include sterile fil-

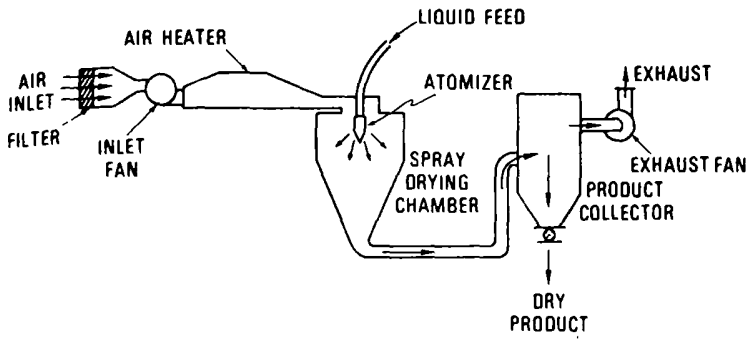

Fig. 13 Schematic drawing of spray-dryer.

tration of very large volumes of air, constructing and maintaining a spray dryer that can be readily sterilized, aseptic transfer of powder from the spray dryer to the powder-filling line, and precise control of the drying conditions to prevent overheating of the product while providing adequate drying. Probably because of these limitations, the technique is not widely used.

E. Protein Formulations

The first biotechnology-derived therapeutic agent to be approved by FDA in the United States was human insulin (Humulin, Eli Lilly) in 1982. The number of such products has grown steadily since then, and now accounts for roughly 3 billion dollars in sales in the United States. This growth is expected to continue during the next decade. Because biotechnology-derived pharmaceuticals are generally proteins and glycoproteins, they require special consideration in formulation and processing.

Special problems with formulation and processing of proteins arise from the hierarchy of structural organization of proteins. In addition to primary structure (the amino acid sequence), proteins have secondary structure (interactions between peptide bonds, resulting in helical or sheetlike structures), tertiary structure (folding of chain segments into a precise three-dimensional arrangement), and in some, quaternary structure (association of individual protein subunits into a multimeric structure). Disruption of this higher-order structure can lead to loss of the biologically active, or native, conformation which, in turn, causes physical instability and may accelerate reactions that are characteristic of chemical instability of proteins.

Loss of the native conformation of a protein generally exposes hydrophobic amino acid residues that are normally buried on the inside of the self-associated structure and are shielded from the aqueous environment. This leads to association between the exposed hydrophobic residues of neighboring proteins (aggregation), or between these exposed residues and hydrophobic surfaces that the protein may encounter either in the manufacturing process or in the primary package.

Processing variables, usually are not critical for traditional low molecular weight drugs, may be critical for protein formulations. For example, vigorous agitation of a protein solution can cause foaming, generating a large air–water interface that is an excellent site for denaturation, aggregation, and perhaps precipitation of protein. Loss of protein by adsorption to surfaces, such as tubing and filters used in manufacturing, can result in subpotent product. Other potentially critical factors in maintenance of the native structure during processing include temperature, pH, the presence of organic solvents, and ionic strength of the formulation.

Disruption of the native structure of a protein can also contribute to chemical instability by accelerating the rates of a variety of degradation routes, including deamidation, hydrolysis, oxidation, disulfide exchange, β-elimination, and racemization.

Formulation strategies for stabilization of proteins commonly include additives such as other proteins (e.g., serum albumin), amino acids, and surfactants to minimize adsorption to surfaces (see Sec. IV.B). Modification of protein structure to enhance stability by genetic engineering may also be feasible, as well as chemical modification such as formation of a conjugate with polyethylene glycol.

Most proteins are not sufficiently stable in aqueous solution to allow formulation as a sterile solution. Instead, the protein is freeze-dried and reconstituted before use. Development of a freeze-dried protein formulation often requires special attention to the details of the freezing process (potential pH shifts and ionic strength increase with freezing) as well as to potential loss of activity with drying. Formulation additives, such as sugars and polyhydroxy compounds, are often useful as cryoprotectants and lyoprotectants (see also Sec. IV.B). Residual moisture may also be critical to the stability of the dried preparation [33].

F. Novel Formulations

A summary of sustained- and controlled-release parenteral dosage forms is included in Chapter 16. This subject is also covered extensively by Chien [34].

Concepts in drug delivery that have received increasing attention include drug carrier systems, implants, intravenous infusers, and implantable infusion pumps. Carrier systems include microspheres, liposomes, monoclonal antibodies, and emulsions. Drugs are incorporated into these systems to increase the duration of drug action and to provide selective delivery of the drug to a specific target site or organ. Implants are used for the same reason. Unwanted side effects and adverse reactions are usually reduced because of selective delivery, which also results in a lower concentration of drug required to achieve the desired therapeutic effect. Infusion pumps provide a delivery system with uniform, continuous flow. A specific dose of a drug, such as insulin, may be administered to a patient on a continual or intermittent basis.

VI. PACKAGING

Container components for parenteral products must be considered an integral part of the product because they can dramatically affect product stability, potency, toxicity, and safety. Parenteral dosage forms, especially solutions, usually require more detailed evaluation of packaging components for product compatability and stability than do other pharmaceutical dosage forms. Common container components in direct contact with the product include various types of glass, rubber, plastic, and stainless steel (needles)—all of which may react with the drug. Maintenance of microbiological purity and product stability, adaptability to production operations and inspections, resistance to breakage and leakage, and convenience of clinical use are factors that must be evaluated when selecting the container.

Parenteral packaging includes ampoules (glass-seal), rubber-stoppered vials and bottles, plastic bags and bottles, glass and plastic syringes, and syringe–vial combinations. Glass containers have traditionally achieved widespread acceptability for parenteral products because of their relative inertness. In recent years, hospital preference for unit-dose and clinical convenience has resulted in an increase in products packaged in disposable syringes and the development of polyvinyl chloride, polyester, and polyolefin plastic containers for IV fluids. Package systems, such as the dual chamber plastic container and Add-Vantage, have been developed for

Fig. 14 Dual-chamber Nutri-Mix container for amino acid and dextrose solutions.

combining unstable mixtures of drugs and solutions (Figs. 14 and 15). Several antibiotics that are unstable in solution are now available as a frozen product in a plastic container. These systems are designed for convenience and cost efficiency as well as minimizing the potential of contamination when preparing the admixture. Parenteral packaging materials are discussed in Chapter 18.

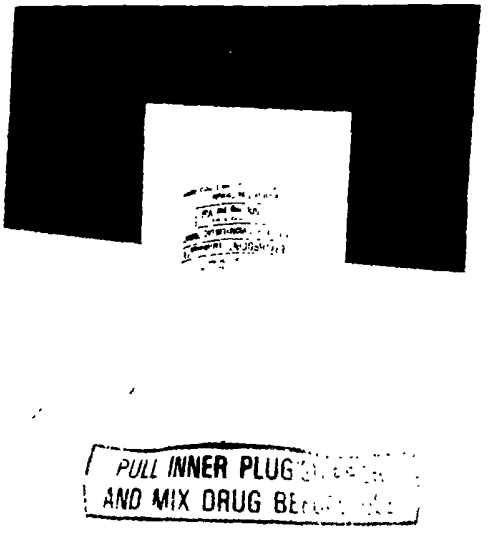

Fig. 15 Add-Vantage drug-diluent admixture system.

VII. STABILITY

A formal stability program is needed to assure that all critical attributes of any drug product are maintained throughout the shelf life of the product. A validated stability-indicating assay is essential to measure chemical or biological activity, and acceptance criteria should be established before initiating stability studies. Particular attention should be given to developing a detailed protocol for a stability study before preparing stability samples, including assays to be performed, storage conditions, and sampling intervals.

In general, expiration dating is based on the estimated time required for the active compound to reach 90–95% of labeled potency at the specified storage temperature. However, other considerations may limit the shelf life of the product. For example, the shelf life of products containing a preservative may be determined by adsorption of preservative to a rubber closure or another elastomeric component of the container–closure system. The drug substance itself may be subject to physical instability such as adsorption. The stability program should include placing enough units at the specified storage conditions to allow inspection of a statistically valid number of units to verify acceptable appearance of the product, such as the development of haze or discreet particulate matter in solution products, as well as to check for discoloration or any other physical attribute that would result in unacceptable pharmaceutical elegance. Formulation pH is often a critical attribute that must be monitored during a stability study, since pH may be affected both by chemical reactions in solution or by interactions between the formulation and the container–closure system.

Sterile powders may require special attention to identify which tests are required to assure adequate physical and chemical stability. The stability of many dried products is often sensitive to small differences in the amount of residual water present, requiring monitoring of residual moisture by Karl Fisher titration or loss on drying. This is particularly important for protein formulations. Special efforts may be needed to minimize the residual moisture in rubber stoppers, since water vapor can transfer from the closure to the powder during prolonged storage. Reconstitution time—the amount of time required after addition of diluent until all solids are dissolved—should be measured routinely. For freeze-dried products, cake shrinkage with time is not uncommon. This may be accompanied by discoloration, increased reconstitution time, or crystallization of one or more component of the formulation. The physical state of the drug—crystalline or amorphous—has an important influence on stability, particularly for cephalosporins. Periodic examination of stability samples by x-ray diffraction may be valuable to identify changes in physical state of either drug or excipients that could influence critical quality attributes. For some solid dosage forms subject to oxidative degradation, it is critical to exclude oxygen from the vial headspace. The headspace of selected vials should be analyzed periodically for oxygen. Many freeze-dried powders are stoppered under vacuum or an inert gas. Testing selected vials during the stability study for presence of vacuum in the headspace of the vial is a useful method of verifying container–closure integrity.

Sterile suspensions can be challenging for physical stability, and this should be reflected in the stability protocol. Examples of physical stability issues for suspensions include (a) caking, which causes poor resuspendability; (b) changes in the particle size distribution, particularly growth of large crystals of drug, which can cause poor syringeability; and (c) polymorphic transformations, which can result in changes in dissolution characteristics and, therefore, the bioavailability of the drug.

For parenteral emulsions, the formulation scientist must be particularly aware of changes in particle size distribution of the oil phase. Droplet coalescence results in increased droplet size. As a general rule, average droplet size should be less than 1 μm. Droplet sizes more than about 6 μm can cause adverse effects.

VIII. STERILIZATION METHODS

Five sterilization processes are described in the *USP* [1]: steam, dry-heat, filtration, gas, and ionizing radiation. All are commonly used for parenteral products, except gas and ionizing radiation, which are widely used for devices and surgical materials. To assist in the selection of the sterilization method, certain basic information and data must be gathered. This includes determining (a) the nature and amount of product bioburden, and (b) whether the product and container–closure system will have a predominately moist or dry environment during sterilization. Both of these factors are of critical importance in determining the conditions (time and temperature) of any sterilization method chosen.

The natural bioburden in a well-maintained pharmaceutical parenteral manufacturing plant is quite low, often to the point that it is difficult to isolate and propagate plant bioburden for sterilization studies. Nevertheless, it is still important to characterize the microbiological bioburden in the process and then monitor it at regular intervals.

For sterilization purposes, microorganisms can be categorized into three general categories: (a) easy to kill with either dry or moist heat; (b) susceptible to moist heat, but resistant to dry heat (e.g., *Bacillus subtilis*); or (c) resistant to moist heat but susceptible to dry heat (e.g., *Clostridium sporogenes*). Organisms such as *B. Subtilis* and *C. sporogenes* are often used as biological indicators because they are spore formers of known heat resistance. When used in a known concentration, they will be killed at a reproducible rate. In this manner, when a product has a low bioburden, biological indicator organism(s) can be used at a concentration of 1×10^3 in kill studies to simulate 10^6 kills of natural (environmental) bioburden. Processing and design of container–closure systems for individual products must be reviewed carefully to ascertain whether moist or dry conditions predominate, particularly in difficult-to-reach inner portions of closures. A good review of the use of biological indicators in validating parenteral container–closure systems may be found in Ref. 35.

The *USP* also recommends the use of biological indicators, whenever possible, to monitor all sterilization methods except sterile filtration. Biological indicators are generally of two types. If a product to be sterilized is a liquid, microorganisms are added directly to carefully identified representative samples of the product. When this is not practical, as with solids or equipment to be sterilized, the culture is added to strips of filter paper. The organism chosen varies with the method of sterilization.

Sterilization tests are performed to verify that an adequate sterilization process has been carried out. Validation of the sterilization cycle also gives assurance of process. Sterility is not assured simply because a product passes the *USP* sterility test. As outlined in the *USP*, the sterility test is described in considerable detail, including procedures for sampling, general conditions of the test, and specific procedures for testing solids and liquids. In addition, guidelines for the design of an aseptic work environment are outlined in some detail. Sample limitations, plus the impossibility of cultivating and testing all viable microorganisms that may be present, affect the reliability of sterility tests. Because of these problems, it is necessary to monitor and test sterilization equipment continuously. Reference 35 provides a good review of validation of sterile products.

A. Sterilization by Steam

When drug solutions and containers can withstand autoclaving conditions, this method is preferred to other sterilization methods because moist heat sterilizes quickly and inexpensively. However, judgment must be exercised and experiments run to ensure that the solution and container are permeable to steam. Oils and tightly closed containers, for example, are not normally sterilizable by steam.

SUN EXHIBIT 1070, IPR2024-00107, PAGE 40

Autoclave steam sterilization is a well-established and widely used procedure. Normally, steam enters through the top of the chamber (Fig. 16). Being lighter than air, it remains at the top of the chamber, but steadily and continuously drives the air out of the chamber through the bottom vent throughout the sterilization cycle. The velocity of steam entering the autoclave, the efficiency of water separation from incoming steam, the size of the drain, and the amount of vacuum applied, all are examples of factors that must be controlled to obtain efficient and reproducible steam sterilization in an autoclave. A thorough description of steam sterilization variables and theory can be found in Ref. 36.

With the widespread use of flexible packaging for LVP products, the use of steam sterilization has increased. Compared with the traditional LVP glass bottles closed with rubber stoppers, flexible LVP plastic containers (polyvinyl chloride, polyester, or polyolefin) offer autoclaving advantages. Specifically, (a) a larger surface area is available for heating per unit volume of liquid; (b) if held in a "flattened" position during sterilization, the heat penetration depth required is reduced, resulting in a more uniform thermal mapping of the contents; and (c) shorter heat-up and cool-down periods are required. The net effect is to allow a much shorter sterilization cycle for LVP products packaged in flexible containers, thus exposing the product to less heat, less potential for degradation, and reduced manufacturing costs.

B. Sterilization by Dry Heat

Dry heat is widely used to sterilize glassware and equipment parts in manufacturing areas for parenteral products. It has good penetration power and is not as corrosive as steam. However, heat-up time is slow necessitating long sterilization periods at high temperatures. It is important to allow sufficient circulation around the materials to be sterilized. Metal cans are often used to contain the parts or containers that are to be sterilized.

The two principal methods of dry-heat sterilization are infrared and convection hot air. Infrared rays will sterilize only surfaces. Sterilization of interior portions must rely on conduction. Convection hot-air sterilizers are normally heated electrically and are of two types: gravity or mechanical. In gravity convection units, a fan is used to promote uniformity of heat distribution throughout the chamber.

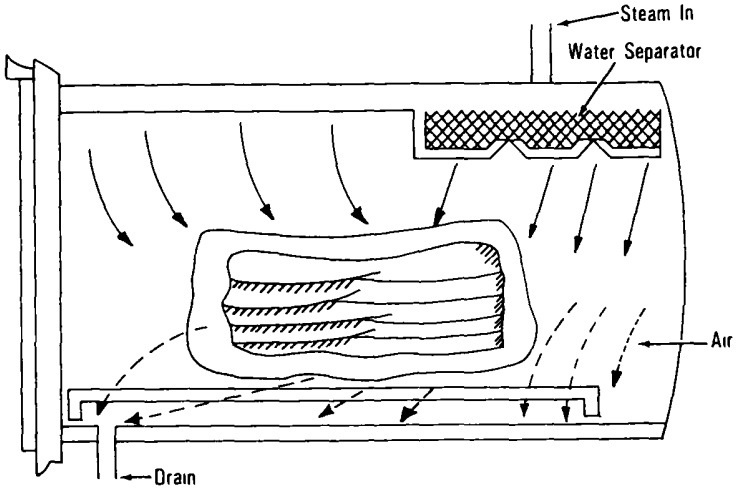

Fig. 16 Gravity displacement steam sterilizer.

Dry-heat processes kill microorganisms primarily through oxidation. The amount of moisture available to assist sterilization in dry-heat units varies considerably at different locations within the chamber and at different time intervals within the cycle. Also, the amount of heat available, its diffusion, and the environment at the spore–air interface all influence the microorganism kill rate. Consequently, cycles tend to be longer and hotter than would be expected from calculations, to ensure that varying conditions do not invalidate a run. In general, convection dry-heat sterilization cycles are run above 160°C [37].

C. Sterilization by Ethylene Oxide

Ethylene oxide (ETO), a colorless gas, is widely used as a sterilant in hospitals and industry for items that cannot be sterilized by steam. It is often diluted with carbon dioxide, or sometimes fluorocarbons, to overcome its flammable and explosive nature. The mechanism by which ETO kills microorganisms is by alkylation of various reactive groups in the spore or vegetative cell. One of the more resistant organisms to ETO is *B. subtilis* var. *niger* (*globigii*). It is the *USP* biological indicator for monitoring the effectiveness of ETO sterilization cycles. Several factors are important in determining whether ETO is effective as a sterilizing gas: gas concentration, temperature, humidity, spore water content, and substrate for the microorganisms. Ethylene oxide should be present at a concentration of about 500 ml/liter for maximum effectiveness. Once gas concentration is not a limiting factor, the inactivation rate of spores by ETO doubles for each 10°C rise in temperature. Relative humidity plays an important role, in that the sensitivity of spores to ETO largely depends on the water content of the spore.

A "typical" ETO sterilization cycle is shown in Fig. 17. As discussed at the beginning of this section, it is important to determine and monitor the bioburden level of the product entering the sterilizer. Also, the load configuration in the sterilizer is important in achieving uniform and reliable sterilization. Unfortunately, commercially available biological indicators used in ETO sterilization are often unreliable. Hopefully, progress will be made in this field in the years ahead.

Unlike other methods, it is necessary to posttreat the product, either through vacuum purging or by allowing the product to remain at ambient conditions for a time, to allow removal of residual ETO and ethylene chlorhydrin/ethylene glycol by-products before use by the consumer.

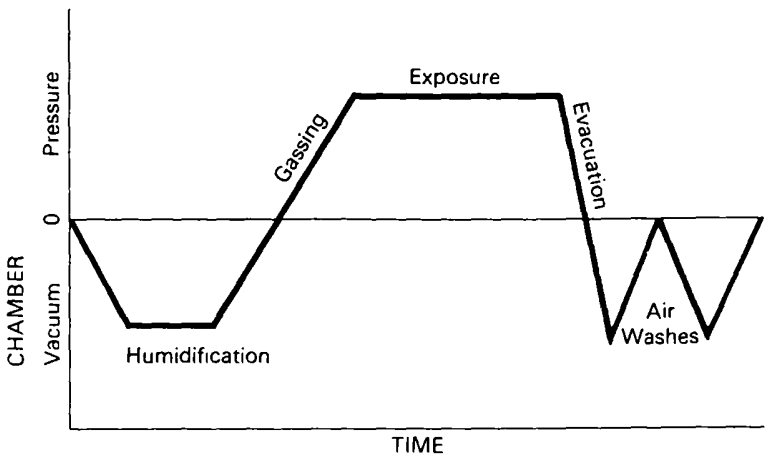

Fig. 17 Ethylene oxide sterilization cycle.

In addition, in 1984 OSHA lowered the maximum permissible operator 8-hr exposure level from 50 ppm in air to 1 ppm (on a time-weighted average) [38].

D. Sterilization by Filtration

It has been only in the past 20 years that filters have become sufficiently reliable to use them on a wide scale to sterilize injectable solutions. Even now, it is prudent to use filtration to sterilize only those products that can not be terminally sterilized.

Filters are of two basic types, depth and membrane. Depth filters rely on a combination of tortuous pathway and adsorption to retain particles or microorganisms. They are made from materials such as diatomaceous earth, inorganic fibers, natural fibers, and porcelain. They carry a nominal rating; that is, a particle size above which a certain percentage of particles is retained. The major advantage of depth filters is their ability to retain large quantities of particles, including many below the nominal rating of the particular filter. Disadvantages of depth filters include grow-through and reproduction of microorganisms, tendency of the filter components to slough during line surges, and retention of some liquid in the filter. Membrane filters rely on sieving and, to a lesser degree, absorption to prevent particles from passing. Although all pores in a membrane filter are not of the same size, nevertheless, the filter can retain all particles larger than the stated size.

Similar to depth filters, membrane filters are made from a variety of materials, although filters made from cellulose ester derivatives are by far the most common. The advantages of membrane filters include no retention of product, no media migration, and efficiency independent of flow-rate pressure differential. The major disadvantages are low capacity before clogging and the need to prewash the filters to remove surfactants. Given the advantages and disadvantages of each type of filter, when large quantities of liquids are to be sterile filtered, such as in industrial applications, it is very common to use a relatively coarse depth filter (1–5 μm) to remove the great majority of particles and, subsequently, use a membrane filter to remove the remaining particles and microorganisms down to a predetermined size (0.22 μm).

Filter cartridges are used for filtering large volumes of solution or more viscous products because of the large surface area that is available through the pleated design. Hydrophobic filters are also available for sterile filtering of gases and solvents [39].

IX. CLINICAL CONSIDERATIONS IN PARENTERAL PRODUCT DESIGN

The formulator must take into consideration all the factors that will improve the clinical acceptability and safety of a product. To minimize tissue damage and irritation and to reduce hemolysis of blood cells and prevent electrolyte imbalance, isotonic solutions should be formulated, if possible. This is not always feasible as a result of the high concentrations of drugs used and the low volumes required for some injections; the wide variety of dose regimens and methods of administration; or because of product stability considerations. Historically, there has been concern over the osmolarity or tonicity of IV fluids. There has also been interest in the osmolarity of other parenteral dosage forms. As mentioned previously, sodium or potassium chloride and dextrose are commonly added to adjust hypotonic solutions.

The effect of isotonicity on reducing pain on injection is somewhat vague, although it may at least reduce tissue irritation. Pain on injection may occur during and immediately following the injection, or it may be a delayed or prolonged type of pain that becomes more severe after subsequent injections. The actual cause of the pain is often unknown and will vary significantly

among patients and according to the product. In some cases, pain may be reduced by minor formulation changes, such as adjusting tonicity and pH, or by adding on anesthetic agent, such as benzyl alcohol or lidocaine hydrochloride. In other cases, pain is more inherent to the drug, and pain reduction is more difficult or impossible to resolve. Pain, soreness, and tissue inflammation are often encountered in parenteral suspensions, especially those containing a high amount of solids.

Thrombophlebitis, which is an inflammation of the venous walls, may occur during IV administration and may be related to the drugs being infused, the administration techniques, the duration of the infusion, and the tonicity, and possibly, the pH of the infusion fluid [40]. It has been difficult to define the relative importance of each because of the interplay of all these variables. Some drugs do cause a more significant amount of phlebitis than others. Perhaps the most important factor is administration technique. Proper cleaning of the injection site, the type of cannula employed, strict adherence to aseptic techniques when one is preparing and administering the fluid, and the duration of the infusion are factors that influence the degree of phlebitis that may occur.

The formulator should be aware of the types of clinical use of a drug when designing the dosage forms. Specific examples are pediatric dosage forms and unit dosage forms—including disposable syringes and special packages for hospital, office, or home administration. Hospital packages can take several forms, depending, for example, on whether the package is to be unit-dose, reconstituted by a nurse, bulk dispensed in the pharmacy, or administered as a secondary "piggyback" IV container.

Drugs that affect tissue properties, particularly blood flow at the absorption site, may be used to control the rate of absorption. Reduced drug absorption may be achieved physiologically with an IM preparation by incorporating epinephrine, which causes a local constriction of blood vessels at the site of injection. Increased muscular activity may enhance drug absorption because of increased drug flow.

When preparing preparations for IV and IM use, the formulator must be aware of the effect of added substances when unusually large doses of the drug are administered. Although the *USP* limits the use of some added substances (Table 4), these types of problems cannot always be anticipated. The *USP* urges special care when administering over 5 ml [1]. When effects do become apparent, the formulator should consider additional dosage sizes or formulation changes. Sometimes during the life of a drug product, new uses and larger doses make the original formula unsatisfactory. When this happens, a new dosage form should be designed and the appropriate cautionary statements placed on the respective labels. The "precautions,

Table 4 Maximum Amounts of Added Substances Permitted in *USP* Injectable Products

Substance	Maximum (%)
Mercury compounds	0.01
Cationic surfactants	0.01
Chlorobutanol	0.5
Cresol	0.5
Phenol	0.5
Sulfur dioxide	0.2
or sodium bisulfite equivalent	0.2
or sodium sulfite equivalent	0.2

SUN EXHIBIT 1070, IPR2024-00107, PAGE 44

problems, hazards, and complications associated with parenteral drug administration'' are discussed extensively by Duma and Akers [41].

All parenteral dosage forms must be sterile, pyrogen-free and essentially free from particles that can be detected by visual inspection. Sources of particulate matter include the drug substance, other components or the vehicle; the manufacturing process, which includes the personnel, environment, equipment; and the packaging components. The *USP* provides methods and standards for a microscopic and an electronic liquid-borne particle counting system for large-volume and small-volume parenterals.

The preparation of a new drug substance or dosage form for evaluation in clinical trials must meet the same regulatory requirements and controls as a marketed product. The cGMP requirements for clinical trial products are outlined by the FDA and are discussed in Chapter 21.

The formulator of a new product must consider the manufacturing process to be used for full-scale production of the product. Many new product failures or deficiencies occur because of the inability to resolve or foresee production-related problems, rather than poor product development per se. Therefore, the scientist who has formulated the product must be involved in the development of its manufacturing process and testing. For example, at scale-up, it was found that there was a loss of preservative in the portion of solution/suspension that was in prolonged contact with the transfer tubing during ''down'' time. This was not observed on a small-scale process with less down time and minimum tubing exposure.

The use of clinical trial manufacture as trial production runs provides valuable information and experience for evaluating the scale-up of the formulation and the process. If validated bulk-drug substance is available during the latter stages of the clinical studies (Phase III), this provides an ideal time to validate the manufacturing process. By using this approach, stability data are included in the validation package, thereby reducing the total amount of stability studies. Also, the validated lots can be used in clinical studies. This also permits a thorough evaluation of the process and specifications before submission of the NDA or the registration document.

A. Toxicity Studies

In toxicity studies, acute toxicity tests are usually carried out in the rat, mouse, cat, and dog. Subacute toxicity studies for IM products are performed by giving SC injections to rats and IM injections to dogs. In IV studies the rat tail vein or a front leg is used. Deliberate overdosing usually ''washes out'' metabolism differences between species. In dogs it is common to give an IV dose five times that intended for humans. In rats this is increased to ten times.

Irritation studies are done in rabbits. Each rabbit serves as its own control. The concentration selected for the irritation studies is that intended for humans.

B. Clinical Evaluation

Clinical evaluation of the dosage form is the most expensive and critical phase of product development. All that has been done before this point has been done in an effort to ensure a safe and reliable product for the clinician.

A drug company normally assigns one of its staff physicians as ''monitoring'' physician for the clinical trial (CT) program. The monitoring physician has the key role in the conduct of the CT program (Fig. 18). He or she coordinates the establishment of clinical protocols, the awarding of grants, the gathering and ''in-house'' evaluation of clinical data, and preparation of the FDA submission.

The monitoring physician must first establish what the clinical protocol is going to be. With injectable products, this involves both a clinical pharmacology safety test and a dose-ranging

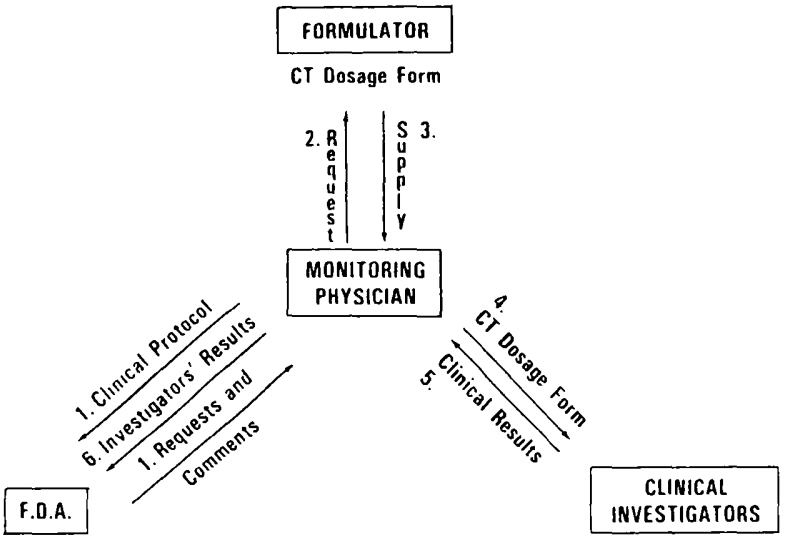

Fig. 18 Clinical trial scheme.

study in humans. These studies are normally a single IM injection in several patients. Depending on the drug, clinical studies may proceed eventually to controlled double-blind studies. Care must be exercised to involve a sufficient number of patients to make the studies statistically meaningful. If it is intended that treatment of several clinical conditions is to be claimed for the product, each must be evaluated separated. Throughout the course of the studies, there is a continuing dialogue between the FDA and the monitoring physician.

When the clinical program has been approved by a peer review committee and filed with the FDA, the monitoring physician requests a sufficient amount of material from the formulator to initiate the clinical program. Before the dosage form is released to the custody of the monitoring physician, the new drug substance and the formulated product must be thoroughly evaluated to ensure proper potency, purity, and safety. Stability studies must also be initiated so that, if the product becomes subpotent or physically unstable during the course of the clinical trial, it can be recalled before any harm can result to the patients in the study.

After release of CT material, the monitoring physician supplies it to the clinical investigators with whom the clinical program has previously been discussed. As the clinical investigators use the product, they begin sending in reports to the monitoring physician, who evaluates them and sends them to the FDA. Although the concept shown in Fig. 18 is oversimplified, it does convey the principal framework under which the clinical trials are conducted.

X. QUALITY ASSURANCE

The terms *quality assurance* and *quality control* are sometimes used interchangeably, but there is an important difference in meaning. Quality control generally refers to testing of raw materials, packaging components, and final product for conformance to established requirements. Quality assurance is a term that includes quality control, but has broader meaning to also include written operating procedures, personnel training, record keeping, and facility design and monitoring. The philosophy of a quality assurance program is to build quality into the product, rather than to rely only on final product testing to cull out defective product.

SUN EXHIBIT 1070, IPR2024-00107, PAGE 46

Although principles of quality control and quality assurance are important to all pharmaceutical dosage forms, they are especially critical when considering the unique attributes of parenteral dosage forms–sterility, absence of pyrogens, and freedom from extraneous particulate matter. Quality control is generally divided into three areas: (a) raw materials, (b) in-process controls, and (c) product specifications. However, numerous attributes for a product have to be considered throughout all phases of development, evaluation, production, and storage to guarantee good quality.

The factors necessary to achieve quality in a product during the developmental stage have been discussed. The formulator of a new product must consider the manufacturing process to be used for full-scale production of the product. Many new product failures or deficiencies occur because of inability to resolve or foresee production-related problems, rather than to poor product development per se. Therefore, the scientist involved in the development of a product must be involved in development of its manufacturing process and testing. Standards must be carefully established for all raw materials and packaging components used in the product so that the quality of the product will be maintained. Trial production runs should be performed on a new product for stability testing and process evaluation.

A. Regulatory and Compendial Requirements

The manufacture and sale of parenteral products is regulated by federal and state laws, as well as by the *USP*. Federal drug regulations are discussed in detail in Chapter 21. The *USP* provides specifications, test procedures, standards, and so on. for parenteral products and their packaging components. In addition to individual monographs, the *USP* limits the use of certain additives (see Table 4), limits the size of multiple-dose containers to 30 ml, and requires a suitable preservative to be added to containers intended for multiple use.

The current Good Manufacturing Practice (cGMP) regulations are guidelines that the FDA requires a pharmaceutical manufacturer to meet. Compliance with the cGMPs is a prerequisite for the approval of NDAs, INDs, and antibiotic forms. General areas in which GMP guidelines must be established and adhered to include:

Organization and personnel
Buildings and facilities
Control of drug components, packaging, and materials
Production and process control
Equipment
Packaging and labeling control
Holding and distribution
Laboratory control
Records and reports

Parenteral formulation and the preparation of parenterals for clinical trial use obviously require adherence to cGMPs. A development group that generates CT materials should have guidelines and written procedures covering such areas as equipment (validation, maintenance, and cleaning), environment (monitoring and cross-contamination), instruments (maintenance and monitoring), housekeeping, documentation, training, and material handling and storage. Sterilization methods, aseptic processing, and filling techniques and methods, all must be validated to assure product sterility and quality. *Validation* is the process of proving that a process or equipment does what it is supposed to do within the established limits. All individuals performing an aseptic process must periodically pass a test to verify their aseptic technique.

SUN EXHIBIT 1070, IPR2024-00107, PAGE 47

B. Monitoring Programs

Process Facilities

Continual evaluation of manufacturing processes are necessary to maintain "good manufacturing practices." Facilities, buildings, and equipment used in the production of parenteral products must be specially designed for this purpose. Factors to be considered when designing a new plant include environmental conditions, work flow, equipment, choice of materials, personnel, organization, process, documentation, production hygiene, and process controls [42,43]. Thorough planning and engineering of a parenteral facility will not only help maintain the quality of the manufactured products, but will simplify cleanup and maintenance requirements. Contamination of a product is minimized by maintaining a clean facility.

Production Areas

Production areas can be separated into seven general classes: cleanup area, preparation area for packaging materials, preparation area for drug products, sterilization facilities, aseptic filling and processing areas, sorting and product holding areas, and a labeling section.

The exact identity of all packaging components, the bulk and filled product, labels, and so on, must be carefully maintained. The production ticket must be written so that it is easily understood and followed by the appropriate production personnel. All procedures should be clearly outlined and limits established for all operators, (e.g., "Heat water to 35–45°C" or "Autoclave sterilize for 15–20 min at 121–124°C).

All production processes, such as ampoule washing and sterilization, solution filtration, equipment setup and operation, sorting, and freeze-drier cleaning and operation, should be covered in detail in a procedure manual to ensure that all operations are understood as well as carried out properly and uniformly. Cleaning, sterilization, sterile filtration, filling, and aseptic processing operations must be validated.

Personnel

People are the principal source of contamination in clean room operations. All personnel involved throughout the development and production of a parenteral product must be aware of those factors that influence the overall quality of a product as well as those factors on which they directly impinge. It is of particular importance that production personnel be properly trained so that human error is minimized. They should be made aware of the use of the products with which they are involved and the importance of following all procedures, especially proper aseptic techniques. Procedures must be set up to check and verify that the product is being manufactured as intended. After manufacture of a batch, production tickets must be carefully checked, sterilization charts examined, and labels verified for correctness and count.

Environmental Monitoring

Control of environmental factors is important to product quality. Air quality and air movement, care and maintenance of the area, and personnel movement and attire are of particular importance.

The air quality in preparation and aseptic areas can be one of the greatest sources of product contamination. However, this problem can be minimized by use of the effective equipment currently available to provide clean air essentially free from microorganisms and dirt particles. Depth-type filters, electrostatic filters, and dehumidification systems are used to remove the major portion of the airborne contaminants. Air for aseptic areas is then passed through high-efficiency particulate air (HEPA) filters, which remove 99.97% of all particles 0.3 μm or larger. To prevent outside air from entering aseptic areas, a positive pressure is maintained relative to corridors.

A laminar flow enclosure provides a means for environmental control of a confined area for aseptic use. Laminar flow units utilize HEPA filters, with the uniform movement of air along parallel lines. The air movement may be in a horizontal or vertical direction and may involve a confined area, such as a workbench, or an entire room. Laminar flow modules are suspended above filling lines, vial- and stopper-washing equipment, and other processes to provide an aseptic and particulate-free environment.

Regardless of the methods used to obtain a clean air environment, unless the parenteral operator is made completely aware of the limits of laminar flow, uses careful, planned movements, and is wearing proper clothing, he or she can be a source of product contamination. Operator movement within aseptic rooms should be minimized. The rooms must be disinfected regularly and thoroughly before setting up for aseptic operation.

Commonly used environmental monitoring techniques include the following:

Passive Air Sampling. Petri dishes containing microbiological growth media are placed in aseptic areas for specified lengths of time, the "settling plates" are then incubated and colonies are counted and identified. This is a qualitative test, since there is no way of knowing the volume of air represented by a given number of colonies.

Active Air Sampling. Active air sampling provides quantitative data because air at a known flow rate is impacted on a strip of nutrient media, followed by incubation of the nutrient strips and enumeration of colonies. Common active air sampling instruments include the slit-to-agar impact sampler and the centrifugal (Reuter) sampler.

Air Classification Measurement. Electronic airborne particle monitoring instruments count and size particulate matter in the sampled air with no consideration of whether the particles are viable or nonviable. Air classification is defined as the number of particles per cubic foot of air that are larger than 0.5 μm in diameter. Climet and HIAC-Royco are common instruments for airborne particulate monitoring).

Surface Monitoring. Contact (or Rodac) plates of growth media are applied to surfaces such as bench tops, walls, and personnel, then incubated. Colony-forming units (CFUs) are counted and identified.

Differential Pressure Measurement. Differential manometers are instruments that measure the difference in pressure between two adjacent rooms. Cleaner environments must have a higher pressure than adjacent less clean environments to prevent flow of relatively dirty air into the cleaner environment. This differential pressure must be monitored and controlled.

C. Product Testing and Evaluation

Quality control testing and evaluation is involved primarily with incoming raw materials, the manufacturing process, and the final product. Testing of incoming raw materials includes routine testing on all drugs, chemicals, and packaging materials.

Process controls include daily testing of water for injection (USP), conformation of fill doses and yields, checking and approving intermediate production tickets, and checking label identity and count. Finished product control includes all the tests necessary to ensure the potency, purity, and identity of the product. Parenteral products require additional tests, which include those for sterility, pyrogens, clarity, and particulate analysis; and for glass-sealed ampoules, leaker testing.

Sterility Testing

The purpose of a sterility test is to determine the probable sterility of a specific batch. The *USP* lists the procedural details for sterility testing and the sample sizes required [1]. The *USP*

official tests are the direct (or culture tube inoculation) method and the membrane filtration method.

The interpretation of sterility results is divided into two stages by the *USP* relative to the type of sterility failure if one occurs. If sterility failure of the test samples occurred because of improper aseptic technique or as a fault of the test itself, stage 1 may be repeated with the same sample size. Sample size is doubled in a stage 2 testing, which is performed if microbial growth is observed in stage 1 and there is no reason that the test was invalid. The only absolute method to guarantee the sterility of a batch would be to test every vial or ampoule.

There is a probability of non-product-related contamination in the order of 10^{-3} when performing the sterility test because of the aseptic manipulations necessary to carry out the procedure. This level (10^{-3}) is comparable with the overall efficiency of an aseptic operation. Confidence in the sterility test is dependent on the fact that the batch has been subjected to a sterilization procedure of proved effectiveness. Records of all sterility tests must be maintained, as well as temperature recordings and records from autoclaves, ovens, or other equipment used during the manufacturing process. All sterilizing equipment must be validated to ensure that the proper temperatures are obtained for the necessary time period. These validations are obtained by the use of thermocouples, chemical and biological indicators, sealed ampoules containing culture medium with a suspension of heat-resistant spores, and detailed sterility testing.

Pyrogen Testing

Pyrogenic substances are primarily lipid polysaccharide products of the metabolism of microorganisms; they may be soluble, insoluble, or colloidal. Pyrogens produced by gram-negative bacilli are generally the most potent. Minute amounts of pyrogens produce a wide variety of reactions in both animals and humans, including fever, leukopenia, and alterations in blood coagulation. Large doses can induce shock and eventually death.

Pyrogens readily contaminate biological materials because of their ability to withstand autoclaving as well as to pass through many filters. Several techniques are used to remove them from injectable products. The ideal situation is one in which there are no pyrogens present in the starting materials. This is achieved by strict control of the cleanliness of equipment and containers, distillation of water, and limited processing times. In general, pyrogens may be destroyed by being subjected to prolonged heating. Other pyrogen-removal techniques, which are generally less effective or applicable, include filtration, absorption or adsorption, chemical (oxidation), aging, or a combination of these.

One pyrogen test is a qualitative biological test based on the fever response of rabbits. If a pyrogenic substance is injected into the vein of a rabbit, a temperature elevation will occur within 3 hr. Many irritative medical agents will also cause a fever.

A preferred method for the detection of pyrogens is the limulus amebocyte lysate (LAL) test. A test sample is incubated with amebocyte lysate from the blood of the horseshoe crab, *Limulus polyphemus*. A pyrogenic substance will cause a gel to form. This is a result of the clottable protein from the amebocyte cells reacting with the endotoxins. This test is more sensitive, more rapid, and easier to perform than the rabbit test.

Leaker Testing and Sealing Verification

Ampoules that have been sealed by fusion must be tested to ensure that a hermetic seal was obtained. The leaker test is performed by immersing the ampoules in a dye solution, such as 1% methylene blue, and applying at least 25 in. (ca. 64 cm) of vacuum for a minimum of 15 min. The vacuum on the tank is then released as rapidly as possible to put maximum stress on weak seals. Next, the ampoules are washed. Defective ampoules will contain blue solution.

Another means of testing for leakers is a high-frequency spark test system developed by the Nikka Densok Company of Japan, which detects the presence of pinholes in ampoules.

Some advantages of this system include higher inspection accuracy, higher processing speed, and eliminating the possibility of product contamination [44].

Bottles and vials are not subjected to such a vacuum test because of the flexibility of the rubber closure. However, bottles that are sealed under vacuum may be tested for vacuum by striking the base of the bottle sharply with the heel of the hand to produce a "water hammer" sound. Another test is the spark test, in which a probe is applied outside the bottle. When it reaches the air space of the bottle, a spark discharge occurs if the headspace is evacuated.

The microbiological integrity of various packages, such as vials and stoppers, disposable syringes, and plastic containers, should be determined. A microbiological challenge test is performed by filling the package with a sterile medium and then exposing the sealed container to one of the following tests that is appropriate for the package system: (a) static-aerosol challenge, (b) static-immersion challenge, (c) static-ambient challenge, or (d) dynamic-immersion challenge. The static-immersion challenge test is used commonly with new package combinations. The sealed containers are periodically challenged by immersion into a suspension of challenge organisms. Storing the containers at 5° or 40–50°C, or both, before immersion provides additional stress.

Clarity Testing and Particulate Analysis

Clarity is defined as the state or quality of being clear or transparent to the eye. Clarity is a relative term subject to the visual acuity, training, and experience of the sorter. Clarity specifications are not given in the *USP*, other than to state that all injections be subjected to visual inspection.

Particulate matter is defined in the *USP* as extraneous, mobile, undissolved substances, other than gas bubbles, unintentionally present in parenteral solutions. Test methods and limits for particulates are stated in the *USP* for large-volume injections and small-volume injections.

The development of sorting standards is the responsibility of the manufacturer. Parenteral solutions are sorted for foreign particles, such as glass, fibers, precipitate, and floaters. The sorter also checks for any container deficiency and improper dose volume when feasible. All products containing clear solutions should be inspected against a black and sometimes a white background using a special light source. Although manual visual inspection is the most common means of inspection, electronic particle detection equipment and computer-controlled electro-optic systems are replacing manual inspection and use a light source or camera, or both, positioned behind, above, or below the units being inspected.

Instruments that measure scattered light, such as the Photo-Nephelometer (Coleman Instruments, Oak Brook, IL) are used to evaluate and set clarity standards for parenteral preparations. It is not possible to establish an overall standard value for all products (e.g., 30 nephelos) because the value itself is relative and influenced by many factors, including concentration, aging, stopper extracts, and the solubility characteristics of the raw materials. Nephelometer readings are insensitive to contamination by large (visible) particulates.

The significance of particulate contamination in all parenteral preparations and devices has received much attention. Although it has not been established that particles can cause toxic effects, the pharmaceutical industry, the medical profession, hospital pharmacists, and the FDA, all realize the importance of reducing particulate levels in all parenteral products and devices.

Sources of particulate matter include the raw materials, processing and filling equipment, the container, and environmental contamination. Several methods have been developed for identifying the source of particulates in a product so that they may be eliminated or reduced. The most effective method is that of collecting the particulates on a membrane filter and identifying and counting them microscopically. However, this method is time-consuming and not adaptable to in-line inspection. Several video image projection methods for in-line detection

of particles have been developed that provide potential for mechanizing inspection. Electronic particulate counters have been applied to parenterals because of the rapidity at which they do particulate analysis. Their main disadvantages are the lack of differentiation of various types of particulates including liquids such as silicones, and the fact that particle size is measured differently from microscopic analysis. The *USP* tests for particulate matter in injections utilizes both the microscopic and light obscuration methods [1].

Labeling

The package and, in particular, the labeling for parenteral dosage forms are integral and critical parts of the product. The labeling must be legible and clearly identify the drug, its concentration, handling or storage conditions, and any special precautions. The dose or concentration must be prominently displayed when other concentrations of the same drug are marketed. Proper labeling is difficult with the space limitation dictated by small containers used for many parenteral products. Smaller containers have become increasingly popular because of the unit-dose concept.

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