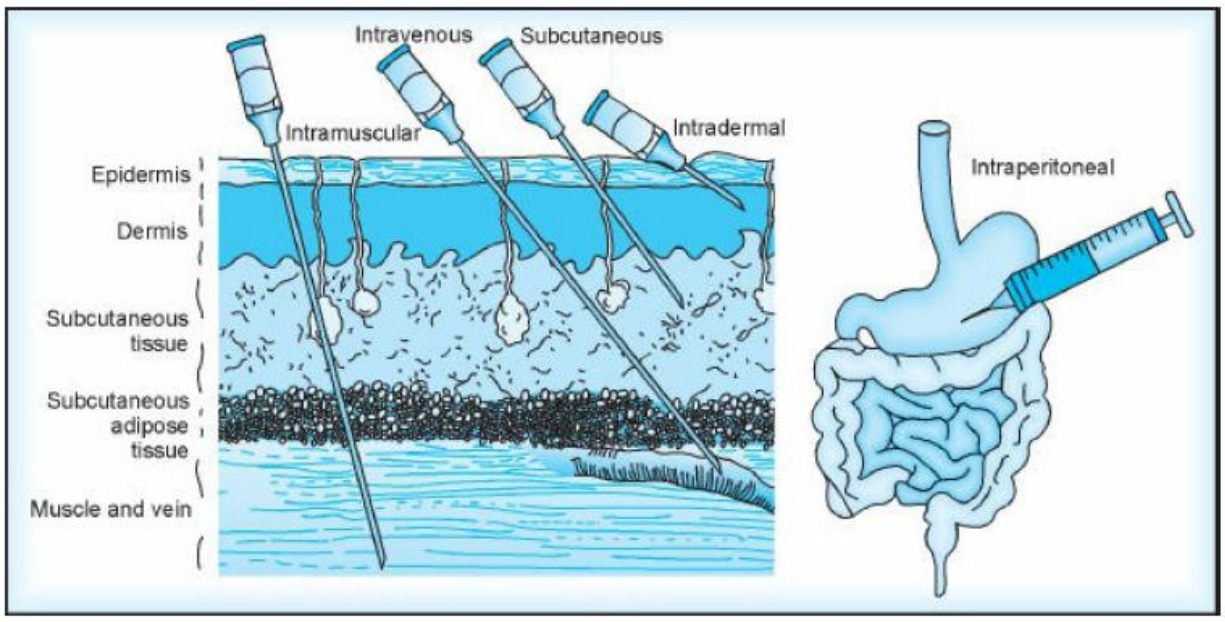
Sterile Products

Sterile products are dosage forms of therapeutic agents that are free of viable microorganisms. Principally, these include parenteral, ophthalmic, and irrigating preparations. Of these, parenteral products are unique among dosage forms of drugs because they are injected through the skin or mucous membranes into internal body compartments. Thus, because they have circumvented the highly efficient first line of body defense, i.e. the skin and mucous membranes, they must be free from microbial contamination and toxic components, as well as possess an exceptionally high level of purity.

All components and processes involved in the preparation of these products must be selected and designed to eliminate, as much as possible, contamination of all types, whether of physical, chemical, or microbiologic origin.

Parenteral preparations may be given by various routes: intravenous,

intramuscular, subcutaneous, intradermal and intraperitoneal.



When injection occurs via an intravascular route, complete drug availability occurs immediately; no absorption is necessary. For all other

routes, at least a blood vessel wall, and usually one or more tissue cell walls,

must be permeated before the drug can enter the circulation. Most often, this

occurs by passive diffusion and is most favourable when the drug has both

lipophilic and hydrophilic properties, with the former being predominant.

With non-vascular injections, absorption is also affected by such factors as the size and number of blood vessels supplying the tissue, the movement (exercise) of the tissue following injection, the physical and chemical properties of the drug and such characteristics of the dosage form as whether it is a solution, suspension, or emulsion, the nature of the vehicle, and its pH. Once in the circulating blood, the physiologic effect of a therapeutic agent is affected by the extent to which it distributes throughout the body, by the degree of binding to plasma proteins and by its rate of elimination by hepatic metabolism and/or renal excretion.

Intravenous and intraspinal preparations are rarely given in a form other than aqueous solutions. The danger of blockage of fine capillaries, particularly in the brain, precludes the use of forms other than solutions for IV administration, although emulsions have been given in which the particle size of the dispersed phase is carefully controlled. The sensitivity of the nerve tissues generally precludes the use of anything but the purest of solutions for intraspinal medication. Preparations given intramuscularly, subcutaneously, or intradermally can be administered as solutions, suspensions, or emulsions.

Even solid pellets may be implanted subcutaneously or intramuscularly. The vehicles can range from Water for Injection, to glycols, to fixed oils. Although care must be exercised to avoid undue tissue irritation, mild local irritation is permissible at these injection sites.

The nature of a preparation can influence significantly the rapidity of onset of a therapeutic effect from a drug, the duration of the effect, and the form of the absorption pattern achieved. Therefore, the development of the formulation for a parenteral product must be integrated carefully with its intended administration in a patient.

The chemical and physical properties of a drug must be determined, its interaction with any desired excipients must be studied, and the effect of each step of the process on its stability must be studied and understood.

Preparations for the eye, though not introduced into internal bodycavities, are placed in contact with tissues that are very sensitive to contamination. Therefore, similar standards are required for ophthalmic preparations.

Irrigating solutions are now also required to meet the same standards as parenteral solutions because during an irrigation

procedure, substantial amounts of these solutions can enter the bloodstream directly through open blood vessels of wounds or abraded mucous membranes.

EFFECT OF ROUTE OF ADMINISTRATION

The intended route of administration has a marked effect on the formulation of a parenteral product. The volume in which a dose of the drug must be encompassed is one factor to consider. For intracutaneous injections a volume of more than 0.2 ml rarely is used because tissue volume is small and compact; also, absorption is quite slow owing to the lack of blood vessels. Volumes of 1 ml or less may be injected subcutaneously and only occasionally are volumes of more than 2 ml given intramuscularly. Volumes of 10 ml or less may be given intraspinally, but only by the IV route may large volumes be given safely, provided careful control of the rate of administration is undertaken. It is not convenient to administer a volume of more than 20 ml by a syringe, and usually it is not practical to set up an infusion unit for less than 250 ml. Isotonicity is a characteristic that is probably of greatest importance for intraspinal injections because the circulation of the cerebrospinal fluid is slow, and disturbances of osmotic

pressure quickly cause headache and vomiting. Since intracutaneous injections are given mostly for diagnostic purposes, nonisotonic solutions may cause false signs of irritation. Isotonicity is preferable for the comfort of the patient, but is not essential for SC and IM injections. For the rapid absorption of drugs given intramuscularly, a slightly hypertonic solution may increase the rate by causing local effusion of tissue fluids. Usually, IV fluids should be isotonic, although slow administration of a paratonic solution may be performed safely if rapid dilution with the blood occurs.

In general, only solutions of drugs in water may be given intravenously. Suspensions may not be given because of the danger of blockage of the small blood vessels. Aqueous or oleaginous suspensions and oleaginous solutions cannot normally be given subcutaneously because of the pain and irritation caused. Muscle tissue tolerates oils and suspended particles fairly well and is therefore the only route normally suitable for their administration.

The administration of a drug deep into the muscle tissue results in a pool of the product at the site of injection. From this depot,

the drug is released at a rate determined to a large extent by the characteristics of the formulation.

Whether the solvent is aqueous or oleaginous affects the rate of absorption; oleaginous solutions are usually more slowly absorbed. Increasing the viscosity of solutions slows the absorption, just as gelatin or polyvinylpyrrolidone in water and aluminum monostearate in oils. Utilizing modifications of the drug molecule to render it less soluble (for instance, the formation of various esters or salts) permits the production of stable suspensions, causing a marked reduction in the rate of absorption of the drug from the depot. Thus, utilizing various modifications in formulation of the product makes it possible to retard the rate at which a drug is released from a depot.

Ophthalmic preparations are formulated in much the same way as parenteral solutions. The eye is particularly sensitive to irritation; therefore, formulation should be directed towards minimizing irritation. Normally, clean aqueous solutions are preferable for ophthalmic use. Suspensions of solids have been used in the eye when the therapeutic need superseded the need to avoid irritating effects, as for the suspensions of corticosteroids used occasionally. It has been found that a

foreign body sensation increases as the concentration of suspended particles, regardless of size, approaches 5%.

Sterile products are most frequently solutions or suspensions, but may even be solid pellets for tissue implantation. The control of a process to minimize contamination for a small quantity of such a product can be achieved with relative ease. As the quantity of product increases, the problems of controlling the process to prevent contamination multiply. Therefore, the preparation of sterile products has become a highly specialized area in pharmaceutical processing. The standards established, the attitude of personnel and the process control must be of a superior level.

FORMULATIONS

Ophthalmic Preparations

Products to be instilled into the eye, while not parenterals by definition, have many similar, and often identical, characteristics. The formulation of stable, therapeutically-active ophthalmic preparations requires high purity of ingredients as well as freedom from chemical, physical (particles), and microbial contaminants. These preparations usually require buffers to stabilize the pH of the product, additives to render it

isotonic or nearly so, and stabilizers such as antioxidants when appropriate for the particular ingredients. Those ophthalmics used in larger quantities, such as eye irrigants, or in the case of devices such as contact lenses, are usually relatively uncomplicated solutions similar to large-volume parenterals. One characteristic not as critical for ophthalmics is freedom from pyrogens since pyrogens are not absorbed systemically from the eye; however, insofar as pyrogens are indicative of a microbiologically clean process, they should not be present.

Freeze-dried Products

Solutions intended to be freeze-dried must be aqueous, for the drying process involves the removal of water by sublimation. Since the solution is in existence for only a brief period during processing, stability problems related to the aqueous system are practically nonexistent. However, the formulation must reflect the characteristics to be imparted to the solid residue (cake) after drying, and those required of the solution after reconstitution at the time of use. Often, the drug alone does not give sufficient solid residue or the characteristics appropriate for the product; therefore, substances often must be added to provide the characteristics desired.

Among the characteristics required of a good cake are (1) a uniform colour and texture, (2) a supporting matrix of solids sufficient to maintain essentially the original volume after drying and (3) sufficient strength to prevent crumbling during storage. In addition, the nature and amount of solids in the solution largely determine (1)the eutectic temperature of the frozen solution, the subzero temperature at which the frozen material will melt, which determines the temperature below which the product must be held during freeze-drying, (2) the rate of thermal and vapour transfer through the product during the process of drying and (3) the rate of solution of the product during reconstitution.

The percentage of solids in the frozen plug should be between approximately 2 and 25%.Among the best salts for providing uniform crystal size, uniform colour and texture, physical strength, and rapid reconstitution are the monobasic and dibasic sodium phosphates. Sodium chloride is often used, but when used alone, the cake tends to shrink markedly in volume and to appear crusty and crumbly. When organic substances, such as mannitol, sorbitol, sucrose, and gelatin are used to provide solids for the cake, care must be taken during the heating, particularly

during the terminal stages of drying, to avoid discolouration of the cake by charring. Added substances required in the formulation must not be volatile under the conditions of drying; therefore, antibacterial agents such as phenol, chlorobutanol, and benzyl alcohol should not be used.

Long-acting Formulations

Long-acting parenteral drug formulations are designed, ideally, to provide slow, constant, and sustained release of a drug over a prolonged period of time, essentially to simulate and replace the more hazardous, continuous i.v. infusion of a drug.

In one type of depot formulation, which is referred to as "dissolution controlled," the rate of drug absorption is controlled by the slow dissolution of drug particles, with subsequent release to tissue fluid surrounding the bolus of product in the tissue. The formation of drug salts with very low aqueous solubility is one of the most common approaches to this type of formulation. Control of the particle size also can contribute to slow dissolution in that larger particles or crystals dissolve more slowly than small crystals with proportionately more surface area. Further, the suspension of the drug particles in vegetable

oils, and especially if gelled with substances such as aluminum monostearate, produces prolonged absorption rates.

Another type of depot formulation is produced by the binding of drug molecules to adsorbents. Only the free portion, in equilibrium with that which is bound, can be absorbed. As drug is absorbed, a shift in equilibrium is established, and the drug is slowly released from the bound state to the free state. This is particularly exemplified by the binding of vaccines to aluminum hydroxide gel to provide a sustained release. A third type of depot preparation is the encapsulation type, in which biodegradable or bioabsorbable macromolecules such as gelatin, phospholipids, and long-chain fatty acids become a diffusion matrix for the drug. The drug is encapsulated within the matrix, and release of drug molecules is controlled by the rate of permeation out of the diffusion barrier and by the rate of biodegradation of the barrier macromolecules. A fourth type is the esterification type depot preparation, in which esters of a drug that are bioerodible are synthesized.

The esterified drug is deposited in tissue at the site of injection to form a reservoir of drug. The rate of drug absorption is controlled by the partitioning of the drug esters from the

reservoir to tissue fluid and by the rate at which the drug ester regenerates the active drug molecule. Often, these esters are dissolved or suspended in oleaginous vehicles, which further slow the release.

Suspensions: The solids content of parenteral suspensions usually ranges between 0.5 and 5%, but may go as high as 30% in some antibiotic preparations. The amount of solids and the nature of the vehicle determine the viscosity of the product, an important factor because of syringeability, the facility with which the product is passed in and out of a syringe. The property of thixotropy is sometimes utilized, particularly with oleaginous suspensions, to provide the sedimentation stability of a gelled preparation during storage and the syringeability of a fluid at the time of administration.

Probably the most important requirement for parenteral suspensions is a small and uniform particle size.

The stabilization of a suspension for the period between manufacture and use presents a number of problems. As indicated, solids gradually settle and may cake, causing difficulty in redispersion prior to use. Surface active agents may aid in the preparation and stabilization of a suspension by

reducing the interfacial tension between the particles and the vehicle. Polysorbate 80, lecithin, Emulphor EL-620 and Pluronic F-68 are among thesurface active agents that have been used in parenteral suspensions. The concurrent addition of a hydrocolloid, such as sodium carboxymethylcellulose, may enhance the effect of the surfactant and cause loss of surface charge of the dispersed particles, water repellency, and the tendency to agglomerate. The following is an example of such a formulation:

Cortisone acetate, microfine	25 mg
Polysorbate 80 (surface active agent)	4 mg
Sodium CMC (protective colloid)	5 mg
Sodium chloride (for tonicity effect)	9 mg
Benzyl alcohol (antibacterial)	9 mg
Water for Injection, to make	1 ml

Emulsions:

The principal problem in the formulation of parenteral emulsions is the attainment and maintenance of uniform oil droplets of 1 to 5 μm in size as the internal phase. With emulsions, separation of the phase does not occur as readily as with suspensions because the difference in density between the oil and water is relatively small. One such product, an emulsion

of a natural vitamin K1, has been stabilized with lecithin.

The preparation of a parenteral emulsion is troublesome. It is made more difficult by the rigid requirement for particle size control to prevent emboli in blood vessels, by the limited choice of emulsifiers and stabilizers of low toxicity, and by the preservation of the oil phase against the development of rancidity.

FORMULATION DEVELOPMENT

The formulation of a sterile product involves the combination of one or more ingredients with a medicinal agent to enhance the convenience, acceptability, or effectiveness of the product. Rarely is it preferable to dispense a drug singly as a sterile dry powder unless the formulation of a stable liquid preparation is not possible.

Therapeutic Agent

A therapeutic agent is a chemical compound subject to the physical and chemical reactions characteristic of the class of compounds to which it belongs. Therefore, a careful evaluation must be made of every combination of two or more ingredients to ascertain whether or not adverse interactions occur, and if they do, of ways to modify the formulation so that the reactions

are eliminated or minimized. The formulation of sterile products is challenging, with respect to the knowledge and ingenuity of the persons responsible.

The amount of information available to the formulator concerning the physical and chemical properties of a therapeutic agent, particularly if it is a new compound, is often quite meager. Information concerning basic properties must be obtained, including molecular weight, solubility, purity, colligative properties, and chemical reactivity, before an intelligent approach to formulation can begin. Improvements in formulation are a continuing process, since important properties of a drug or of the total formulation may not become evident until the product has been stored or used for a prolonged time. However, because of the extensive test documentation required by the US Food and Drug Administration (FDA), only outstanding formulations can be justified for continuance to the state of a marketed product.

Vehicles or Solvent System

Aqueous Systems: the most frequently employed vehicle for sterile products is water, since it is the vehicle for all natural body fluids.

One of the most inclusive tests for the quality of water is the total solids content, a gravimetric evaluation of the dissociated and un-dissociated organic and inorganic substances present in water. the 10 ppm total solids officially permitted for Water for Injection may be much too high when used as the vehicle for many products. Water shall contain a minimal amount of organic compounds. Such compounds are undesirable for two main reasons: they may be toxic, and/or they may serve as sources of nutrition for microorganisms. In practice, Water for Injection normally should not have a conductivity of more than 1micromho (1 megohm, approximately 0.1 ppm NaCl) and total organic carbon (TOC) not more than 500 ppm.

Non-aqueous and Mixed Solvents:

In the formulation of sterile pharmaceutical products, it is sometimes necessary to eliminate water entirely or in part from the vehicle, primarily because of solubility factors or hydrolytic reactions.

Water-immiscible solvents include fixed oils, ediyl oleate, isopropyl myristate, and benzyl benzoate. The most frequently used non-aqueous solvents are polyediylene glycol, propylene glycol, and fixed oils.

Solvent selection: A parenteral therapeutic agent is given by preference as a solution. If aqueous, the solution is physiologically compatible with body tissues, and the biologic response elicited should be reasonably predictable.

The high dielectric constant of water makes it possible to dissolve ionizable electrolytes, and its hydrogen bonding potential brings about the solution of such organic substances as alcohols, aldehydes, ketones, and amines. Conversely, water is a poor solvent for nonpolar compounds, such as alkaloidal bases, which require non-polar solvents. Since therapeutically active compounds given by injection range in property from highly polar to non-polar, solvents having complementary properties must be employed if a solution is to be achieved. Adding to the complexity of solvent selection, is the requirement that solvents to be injected must be of low toxicity to body tissues. Ether is a solvent for testosterone, but is highly irritating to body tissues and cannot be used alone as a solvent for an injectable preparation. Frequently, the desired solubility can be achieved with mixed solvents, e.g. the use of approximately 40% ethanol in water to solubilize the digitalis glycosides.

Compounds that are dissolved in water are often subject to degradativereactions, such as hydrolysis, oxidation, decarboxylation, and racemization.Formulation must be designed, in such cases, to minimize the degradative effects. Often, these reactions are markedly affected by the pH of the solution. Epinephrine in solution undergoes racemization and oxidation, but if the pH is maintained at 3.0 or less, little reaction occurs. The oxidation reaction can be further reduced by displacing atmospheric oxygen with an inert head space gas and adding 0.1% (w/v) sodium metabisulfite as an antioxidant. Atropine sulfate rapidly hydrolyzes in solution, but if the pH is maintained with a buffer system at about 3.5 to 4.0, hydrolysis does not occur at a significant rate.

The use of a mixed solvent system often reduces degradative reactions.Barbituric acid derivatives hydrolyze readily in water, particularly at a lowpH. It has been shown, however, that pentobarbital sodium is soluble and stable in a vehicle containing 60% polyethylene glycol 400 and 10% ethanol in water at a pH of 8.

The aforementioned reactions do not occur in an anhydrous, non-polar vehicle, such as fixed oil, although the presence of a

small amount of water may permit slight reactions. Oleaginous injections are subjected, however, to the disadvantages of being viscous (thus difficult to administer, particularly in cold weather) and of involving frequent incidence of pain upon injection.

Solutes

The physical and chemical purity of solutes used for sterile preparations must also be exceptional. Obviously, the contaminants entering a product with a solute have the same effect as if they entered via the vehicle. Even small traces of contaminants may be detrimental to products, necessitating purification of the solute. For a few substances (for example, ascorbic acid and calcium gluconate), special parenteral grades are commercially available.

In addition, solutes should be free from microbial and pyrogenic contamination. This entails not only proper quality of the chemical as procured, but also storage conditions designed to prevent contamination, particularly after a container has been opened. Preferably, production lots should be designed to use the entire contents of packages of chemicals whenever possible.

Added Substances

Substances added to a product to enhance its stability are essential for almost every product. Such substances include solubilizers, antioxidants, chelating agents, buffers, tonicity contributors, antibacterial agents, antifungal agents, hydrolysis inhibitors, antifoaming agents, and numerous other substances for specialized purposes. At the same time, these agents must be prevented from adversely affecting the product. In general, added substances must be nontoxic in the quantity administered to the patient. They should not interfere with the therapeutic efficacy or with the assay of the active therapeutic compound. They must also be present and active when needed throughout the useful life of the product. Therefore, these agents must be selected with great care, and must be evaluated as to their effect upon the entire formulation.

Antibacterial agents: Antibacterial agents in bacteriostatic concentration must be included in the formulation of products packaged in multiple-dose vials, and are often included in formulations to be sterilized by marginal processes or made by aseptic manipulation.

Antioxidants: Antioxidants, included in many formulations to protect a therapeutic agent susceptible to oxidation, particularly under the accelerated conditions of thermal sterilization, may function in at least two ways., i.e. (1) by being preferentially oxidized (reducing agents), and thereby gradually used up, or (2) by blocking an oxidative chain reaction in which they are not usually consumed. In addition, certain compounds have been found to act as synergists, increasing the effectiveness of antioxidants, particularly those blocking oxidative reactions. A fourth group of compounds are useful in this connection in that they complex with catalysts that otherwise would accelerate the oxidative reaction. Because of the differences in action, combinations of these agents are sometimes used.

Antioxidants (reducing agents)

Ascorbic acid Sodium bisulfite

Antioxidants (blocking agents)

Ascorbic acid esters Butylated hydroxytoluene (BHT)

Synergists

Ascorbic acid Citric acid

Chelating agents

Ethylenediaminetetraacetic acid salts

It should also be mentioned that for those products in which oxygen enters into a degradative reaction, an antioxidant effect can be achieved by displacing oxygen (air) from contact with the product. Usually, this is accomplished by saturating the liquid with either nitrogen or carbon dioxideand sealing the final container after displacing the air above the product with the gas.

Buffers:

Buffers are added to maintain the required pH for many products, as change in pH may cause significant alterations in the rate of degradative reactions. Changes in pH may occur during storage as a result of the dissolution of glass constituents in the product, release of constituents from rubber closures or plastic components in contact with the product,dissolution of gases and vapours from the airspace in the container and diffusion through the rubber or plastic component, or reactions within the product. Buffers must have the capacity to maintain the pH of the productagainst these influences, but not enough to prevent the body fluids from over whelming the buffer ollowing administration. In most cases, the biologic effectiveness of the drug is maximum at or near the biologic fluid pH rather than at the stabilizing pH of the injected product.

Acetates, citrates and phosphates are the principal buffer systems used, but buffer systems making use of other ingredients in the formulation are often used to reduce the total number of ingredients in the product.

Tonicity contributors:

Compounds contributing to the isotonicity of a product reduce the pain of injection in areas with nerve endings. Various agents are used in sterile products to adjust tonicity. Simple electrolytes such as sodium chloride or other sodium salts and non-electrolytes such as glycerin and lactose are most commonly used for this purpose.

Chelating agents:

Chelating agents may be added to bind, in nonionizable form, trace amounts of heavy metals, which if free, would catalyze degradative changes. The chelating agent most commonly used is the trisodium or calcium disodium salt of ethylenediamine tetra-acetic acid in a concentration of about 0.05% (w/v).

Inert gases:

These have been used to displace oxygen from a solution and reduce the possibility of oxidative changes in the formulation. Inert gases may be used to stabilize solutions in other ways. For

example, sodium bicarbonate injection decomposes, particularly during autoclaving, to produce sodium carbonate, carbon dioxide, and water. Saturation of the solution with carbon dioxide inhibits this reaction and stabilizes the solution.

Protein stabilizers:

A number of ingredients have been shown to stabilize proteins, both in the dry and solution state. Serum albumin competes with therapeutic proteins for binding sites in glass and other surfaces and minimizes the loss of the protein caused by surface binding. A number of different types of substances are used as **cryoprotectants** and **lyoprotectants** to minimize protein denaturation during freeze-drying. Antioxidants, buffers and chelating agents are also used to stabilize proteins in solution when necessary.

CONTAINERS

Glass containers traditionally have been used for sterile products, many of which are closed with rubber stoppers. Interest in plastic containers for parenterals is increasing, and such containers are being used for commercial ophthalmic preparations and IV solutions.

Plastic Containers:

The principal ingredient of the various plastic materials used for containers is the thermoplastic polymer. Although most of the plastic materials used in the medical field have a relatively low amount of added ingredients, some contain a substantial amount of plasticizers, fillers, antistatic agents, antioxidants, and other ingredients added for special purposes. These ingredients are not usually chemically bound in the formulation and, therefore, may migrate out of the plastic and into the product under the conditions of production and storage. Considerable variability also has been encountered in the purity of the commercially available polymers. Plastic containers are used mainly because they are light in weight, are non-breakable, and, when low in additives, have low toxicity and low reactivity with products. Tissue toxicity can occur from certain polymers, but additives are a more common cause. Reactivity due to sorption(absorption and/or adsorption) has been found to occur most frequently with the polyamide polymers, but additives leached from any of the plastic materialsmay interact with ingredients of the product.

Glass Containers

Glass is still the preferred material for containers for injectable products. The two general types of glass are soda-lime and borosilicate. The glass that is most resistant chemically is composed almost entirely of silicon dioxide, but it is relatively brittle and can only be melted and molded at high temperatures. The USP provides the Powdered Glass and the Water Attack tests for evaluating chemical resistance of glass. The test results are measures of the amount of alkaline constituents leached from the glass by purified water under controlled elevated temperature conditions; the Powdered Glass test is performed on ground, sized glass particles, and the Water Attack test is performed on whole containers. On the basis of the results from the official tests, glass compounds are classified into four types. The greatest chemical resistance is provided by Type I, and the least by NP (non-parenteral) glass. It should be noted, however, that within these types, as well as Types II and III.

Type I glass is preferred for most sterile products, but Types II and III may be used when the product has a non-aqueous vehicle or the period of contact with the aqueous vehicle is brief, as with

dry powders reconstituted just prior to use, or if the non-reactivity between the glass and product has been established.

Physical Characteristics

The protection of light-sensitive products from the degradative effect of ultraviolet rays may be one of the important physical characteristics of a glass container. Ultraviolet rays can be completely filtered out by the use of amber glass.

Container use Considerations

Single-dose containers are intended to provide sufficient drug for just one dose, the integrity of the container being destroyed when opened so that it cannot be reclosed and used again. Single-dose containers may range from liter bottles of IV solutions to 1 ml, or smaller, cartridges. The desire for further reduction in the risk of contamination, both bacterial and viral, and an increased control over the administration of drugs, particularly in a hospital, have led to the recent development of single-dose, disposable administration units. For most of these units, the product container is a glass cartridge with plastic and metal fitments separated from immediate contact with the product.

Rubber Closures

Rubber closures are used to seal the openings of cartridges, vials, and bottles, providing a material soft and elastic enough to permit entry and withdrawal of a hypodermic needle without loss of the integrity of the sealed container.

Ideally, closures should be completely nonreactive with the product with which they are in contact. No such ideal compound exists; therefore, each rubber compound should be tested for compatibility with each preparation with which it is to be used. Two general compatibility problems exist, namely, the leaching of ingredients from the rubber compound with subsequent reaction with ingredients of the product, and the removal of ingredients from the product by sorption by the rubber compound or by vapour transfer through the closure.

Several properties of rubber closures are significant, particularly elasticity, hardness, and porosity. Rubber closures must be sufficiently elastic to provide a snug fit between the closure and the neck and lip of the glass container.

Devices

Devices associated with sterile products include the following:

Administration sets for large volume parenterals (LVPs)

Filter needles

Hypodermic needles

Hypodermic syringes

In-line filters

Plastic irrigating solution bottles

Plastic LVPs containers

Plastic ophthalmic dropping bottles

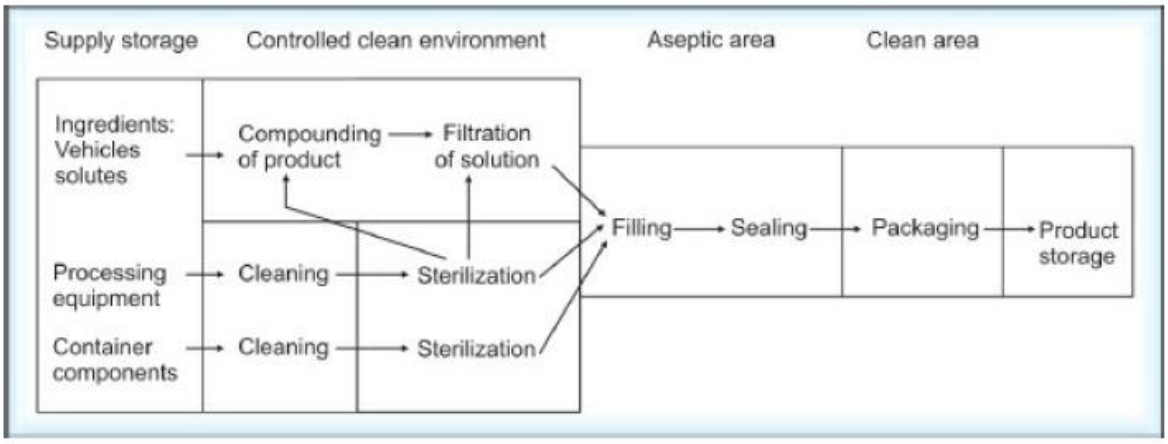
Transfer needles

Transfer sets

Although the contact time of the product with the device is usually brief, it is intimate; therefore, compatibility between the device and the product must be evaluated. For example, it has been shown that insulin can be adsorbed by PVC tubing during the time of contact for administrative of an IV solution, approximately 6 h.

PRODUCTION

The production process includes all of the steps from the accumulation and combining of the ingredients of the formula to the enclosing of the product in the individual container for distribution. Intimately associated with these processes are the personnel who carry them out and the facilities in which they are performed. The most ideally planned processes can be rendered ineffective by personnel who do not have the right attitude or training, or by facilities that do not provide an efficiently-controlled environment. To enhance the assurance of successful manufacturing operations, all process steps must be carefully reduced to writing after being shown to be effective.



Quality Control

The three general areas of quality control are incoming stock,

manufacturing (processing), and the finished product. For sterile products, incoming stock control encompasses routine tests on all ingredients as well as special evaluations such as pyrogen tests on WFI, glass tests on containers, and identity tests on rubber closures. It also may be necessary to perform microbial load (bioburden) tests to determine the number and types of microorganisms present. Process control in the manufacture of sterile products involves all of the innumerable tests, readings, and observations made throughout the manufacturing process of a product, including conductivity measurements during the distillation of WFI, confirmation of volume of fill in product containers, recording of cycle time and temperature for thermal sterilization of the product, and confirming the count and identity of labels for the product. The production control includes all of the final assays and tests to which the product is subjected. In addition to the usual chemical and biologic tests, a sterile product is subjected to a leak test (when applicable), a clarity test, a pyrogen test (when applicable), and a sterility test.

Leak Test

Ampoules are intended to provide a hermetically sealed container for a single dose of a product, thereby completely

barring any interchange between the contents of the sealed ampoule and its environment.

The leak test is intended to detect incompletely-sealed ampoules so that they may be discarded. Tip-sealed ampoules are more likely to be incompletely sealed than are those that have been pull-sealed. In addition, small cracks may occur around the seal or at the base of the ampoule as a result of improper handling. Vials and bottles are not subjected to such a leak test because the rubber closure is not rigid; however, bottles are often sealed while a vacuum is being pulled so that the bottle remains evacuated during its shelf-life.

Clarity Test

Clarity is a relative term, the meaning of which is markedly affected by the subjective evaluation of the observer. Unquestionably, a clean solution having a high polish conveys to the observer that the product is of exceptional quality and purity. It is practically impossible, however, to prepare a lot of a sterile product so that every unit of that lot is perfectly free from visible particulate matter, i.e. is, from particles that are 30 to 40 μm and larger in size.

Although particulate matter is of primary concern in products given intravenously, all parenteral products should be free from insoluble particles.

Suspensions, emulsions, or dry solids, in addition to solutions, should be compounded and processed under clean conditions to minimize the presence of foreign particles.

The visual inspection of a product container is usually done by individual human inspection of each externally clean container under good light, baffled against reflection into the eyes, and viewed against a black and white background, with the contents set in motion with a swirling action, since a moving particle is much easier to see than one that is stationary.

Pyrogens and Pyrogen Test

Water used in parenteral and irrigating solutions should be free of pyrogens. To achieve this, proper controls must be maintained in the preparation and storage of water. Pyrogens are products of metabolism of microorganisms. Most bacteria and many molds and viruses have been reported as producing pyrogens. The gram-negative bacteria produce the most potent pyrogenic substances as endotoxins. Chemically, pyrogens are

lipid substances associated with a carrier molecule, which is usually a polysaccharide but may be a peptide.

About 1 h after injection into man, pyrogens roduce a marked rise in body temperature, chills, body aches, cutaneous vasoconstriction, and a rise in arterial blood pressure.

Antipyretics eliminate the fever, but not the other systemic effects of pyrogens.

The fever response to pyrogens in rabbits is the basis for the official pyrogen test.

Sterility Test

All products labeled “sterile” must pass the sterility test, having been subjected to an effective process of sterilization. The test for sterility is intended for detecting the presence of viable form of microbes in pharmacopoeial preparations.

Method A: Membrane Filtration

A suitable unit consists of a closed reservoir and a receptacle between which a properly supported membrane of appropriate porosity is placed. A membrane suitable for sterility test has a nominal pore size not greater than 0.45 μm, diameter of approximately 47 mm and whose effectiveness to retain

microorganisms has been established. Cellulose nitrate filters, for example, are used for aqueous, oily, and weakly alcoholic solutions; and cellulose acetate filters, are used for strongly alcoholic solutions. Specially adapted filters may be needed for certain products such as antibiotics.

Method B: Direct Inoculation

Apart from testing oily solutions, creams, ointments and solid products, direct inoculation method is utilized particularly for surgical devices, sterile devices, surgical dressings and sutures, in case where membrane filtration method appears difficult. In this test, the quantity of the preparation to be examined is transferred directly into the culture medium so that the volume of the product is not more than 10% of the volume of the medium, unless otherwise prescribed.