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## A Review on: Parenteral Drug Delivery System



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HUMAN

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### ABSTRACT

The parenteral administration route is the most effective and common form of delivery for active drug substances with poor bioavailability and drugs with a narrow therapeutic index. But parenteral route offers rapid onset of action with rapid declines of systemic drug level. For the sake of effective treatment, it is often desirable to maintain systemic drug levels within the therapeutically effective concentration range for as long as treatment calls for. It requires frequent injection, which ultimately leads to patient discomfort. For this reason, a drug delivery system that can reduce the total number of injections throughout the effective treatment, improve patient compliance as well as pharmacoeconomic. Parenteral drug delivery systems are the preparations that are given other than the oral route. (Para-outside, enteric-intestine). The parenteral drug delivery system seeks to optimize the therapeutic index by providing the immediate drug to the systemic pool in the required quantity to treat cardiac attacks, respiratory attacks. This article includes all the details of the parenteral drug delivery system.

## INTRODUCTION:

In medicine and pharmacy, enteral administration is the term used to describe drug administration by the gastrointestinal tract. Majority of medicines are administered orally by this route in the form of tablets, capsules, or liquids. NDDS is the system for the delivery of drugs other than the conventional route. The enteral route also encompasses rectal administration utilizing dosage forms such as suppositories, or rectal ointment. In novel drug delivery systems, the parenteral route is the most common and effective for delivering the active ingredient, to express its therapeutic activity. A drug delivery system (DDS) is defined as a formulation or a device that enables the introduction of a therapeutic substance in the body and improves its efficacy and safety by controlling the rate, time, and place of release of drugs in the body <sup>[1]</sup>. This process includes the administration of the therapeutic product, the release of the active ingredient by the product, and the subsequent transport of the active ingredients across the biological membranes to the site of action. The term therapeutic substance also applies to an agent such as gene therapy that will induce in vivo production of the active therapeutic agent. Gene therapy can fit in the basic and broad definition of a drug delivery system. Gene vectors may need to be introduced into the human body by novel delivery methods. However, gene therapy has its special regulatory control. A drug delivery system is an interface between the patient and the drug. It may be the formulation of a drug, to administer it for a therapeutic purpose, or a device used to deliver the drug. In practice, however, parenteral administration is commonly taken to mean drug administration by injection. The word parenteral is derived from the two words “para” and “enter on” means to avoid the intestine <sup>[2]</sup> According to USP 24/NF19, the parenteral articles are defined as those preparations intended for injection through the skin or other external boundary tissue, rather than through the alimentary canal, so that the active substances can be administered directly into a blood vessel, organ, tissue, or lesion. In today’s health care scenario, the key component of therapy for hospitalized patients is parenteral products. Parenteral route of administration i.e. Subcutaneous, intramuscular, intravenous, intradermal and intra-arterial, etc. also possess good absorption characteristics and provide good bioavailability of drugs <sup>[3]</sup> The route has a plethora of advantages for patients who cannot take the drug orally and require rapid onset of action i.e. in case of unconscious patients <sup>[4]</sup> Hospitalized and bedridden patients are dependent on parenteral nutrition like fluids, electrolytes, or nutrients by parenteral route. Now a days novel parenteral drug delivery systems like biodegradable implants, transdermal patches, colloidal drug carriers like liposomes, nanoparticles,

intramuscular depot injections, are playing a major role. Novel preparations provide sustained, targeted and controlled drug delivery to the patients with less dosing frequency<sup>[5,6]</sup> Despite so many benefits of parenteral formulations are more expensive and costly than conventional formulations. It requires specialized equipment, devices, and techniques to prepare and administer parenteral formulations<sup>[7]</sup> Despite all these problems, parenteral formulations hold a top place for the treatment of hospitalized patients. Since parenteral products are meant to be introduced directly into the blood for which they should be properly sterile and free from pyrogens.

**PARENTERAL PRODUCTS:** <sup>[8-11]</sup>

Small volume parenterals (SVP) or injections are 100ml or less and can be provided as a single-or multidose product.

Large volume parenterals (LVP) are intended to be used intravenously as a single-dose injection and contain more than 100ml of solution. SVP and LVPs are often combined during the extemporaneous preparation of intravenous admixtures.

**Types of Parenteral preparations:** It can be categorized as <sup>[12]</sup>

Small scale dispensing – Usually one unit at a time.

Large scale manufacturing – In these hundreds of thousands may constitute one lot of products.

**Table No. 1: Difference between Large volume parenteral and small-volume parenteral.**

Parameter	Large volume parenteral	Small volume parenteral
Volume	101 – 1000 ml	100 ml or less
Route	IV	IV, IM, SC
Dose unit	Single	Single or multiple
Needle	1 ½, 18-19 gauze	1 ½, 20-22 gauze
Preservative	Not used	Used
Buffer	Not used	Used
Formulation	Solution and o/w nutrient emulsion	Solution, emulsion, suspension
Use	As nutrition in detoxification Aid during surgery	As therapeutic As diagnostic agents

**Table No. 2: Advantages and Disadvantages of Parenteral Products:<sup>[13]</sup>**

<b>Advantages</b>	<b>Disadvantages</b>
Provides drug and nutritional options for patients unable to tolerate oral therapy	Difficulty/ impossibility of drug removal/ reversal
Circumvents absorption limitations of the gastrointestinal tract	Risk of infection
The quick onset of action	Risk of emboli
Localized delivery	Risk of hypersensitivity reactions
Prolonged duration of effect	Higher costs

**ROUTES OF PARENTERAL ADMINISTRATION:**

Medicines are injected by many different routes and the choice of route is governed by the purpose of the treatment and the volume of medicine to be administered. The different routes are:

1. Intravenous injections and infusions
2. Intra-arterial and intracardiac
3. Intradermal injections
4. Subcutaneous injections
5. Intramuscular injections
6. Intraspinial injections
7. Intra-articular injections
8. Ophthalmic injections



**Intravenous injections and infusions:**

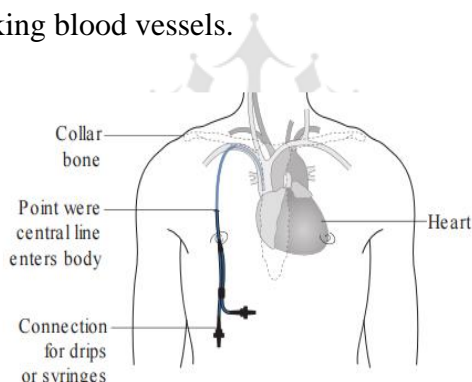
1. Intravenous injections and infusions are administered into an easily accessible prominent vein near the surface of the skin, typically on the back of the hand or in the internal flexure of the elbow.

2. The volumes administered can range from 1ml for intravenous injection, up to several liters for an intravenous.

3. Medicines administered by intravenous injections (or intravenous bolus dose) will rapidly increase the concentration of the drug in the plasma and produce a rapid effect. If the medicine is first added into a large volume of fluid (500ml to 1L infusion bag) and then administered by intravenous infusion at a slow and controlled rate, often utilizing a pump, the drug will enter the circulation at a much slower and controlled rate.

4. Drug solutions at high or low pH or highly concentrated hypertonic solutions will damage the cells lining the vein and cause localized pain and inflammation (thrombophlebitis). To avoid this problem a central line may be inserted.

5. Injections that are formulated either as water in oil emulsion or suspension must not be administered by the intravenous route. This is because the suspended drug particles physically block blood capillaries and the oil phase of a water-in-oil injection could cause a fat metabolism, again blocking blood vessels.



**Figure No. 1: Intravenous injections and infusions**

#### **Intra-arterial and intracardiac injections:**

6. The large majority of drugs that are administered parentally are given intravenously. This delivers the drug directly into the bloodstream to provide a rapid and predictable clinical effect.

7. Arteries are not as readily accessible as veins and this technique is much more invasive and carries a greater risk than simple intravenous administration. For this, it is seldom used.

8. Intra-arterial administration is sometimes used when intravenous access cannot easily be established, such as in very premature infants, due to the very small size of their veins to the catheter tubes used to maintain vascular access.

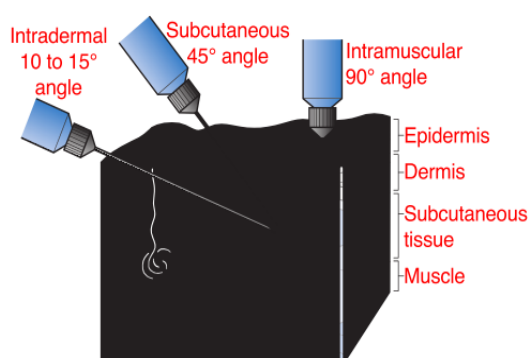
9. Intra-arterial has also been used in the treatment of some cancers (such a liver cancer) where the anti-cancer medicines are injected into an artery upstream of the tumor site to ensure the maximum amount of drug reaches the tumor before distribution anywhere around the body.

10. Intracardiac injections are used to administer a drug (a common example being an aqueous solution of adrenaline) directly into either cardiac muscle or into a ventricle of the heart. This is undertaken only in life-threatening emergencies to produce a rapid, local effect in the heart during a heart attack or in circulatory collapse.

#### **Intradermal injections:**

11. Intradermal injections are given into the skin between the epidermal and dermal layers. Volumes of up to 0.2ml can be given by this route and absorption from the intradermal injection site is slow.

12. This route is used for immunological diagnostic tests, such as allergy tests, or the injection of tuberculin protein to determine immunity against tuberculosis. Some vaccines like BCG (tuberculosis) are administered by intradermal injection.



**Figure No. 2: Intradermal injections**

### **Subcutaneous injection:**

Subcutaneous injections are administered into the loose connective and adipose tissues immediately below the dermal skin layer.

Typical injection sites are the abdomen, upper arms, and upper legs. Volumes of up to 1ml can be administered comfortably, and aqueous solutions or suspensions of drugs are administered by this route.

As this tissue is highly vascular, drugs administered by the subcutaneous route are fairly, rapidly, and predictably absorbed from this site. A common example of a drug administered by subcutaneous injection is insulin.

### **Intramuscular injections:**

Intramuscular injections are preferably administered into the tissue of a relaxed muscle. The muscle sites commonly used for intramuscular injections are the thigh or shoulder muscles.

Aqueous or oily solutions or suspensions can be administered in volumes of up to 4ml.

Drugs administered by the intramuscular route are slowly absorbed from the injection site into the systemic circulation compared to those administered by the subcutaneous route.

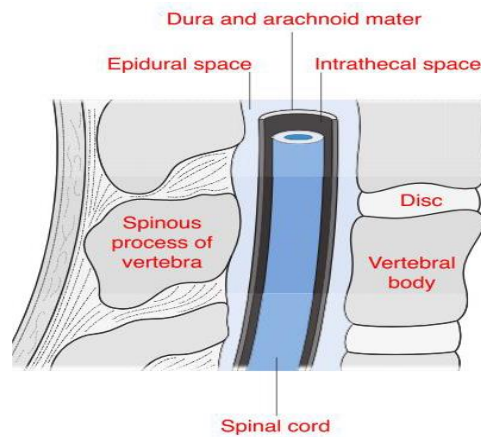
### **Intraspinal injection:**

Intraspinal injections are given between the vertebrae of the spine into the area of the spinal cord. Only drugs in an aqueous solution are administered by this route.

This route can be used for spinal anesthesia. Also, the indication was given to introduce drug substances into the CSF that would otherwise not diffuse across the blood-brain barrier. Typically, this could be antibiotics to treat meningitis or anticancer agents such as methotrexate or cytarabine. Volumes up to 10ml can be administered by Intrathecal injection.

Intracisternal injections are given between the atlas and axis vertebrae into the cisterna magna. This route is also used for antibiotic administration into the CSF, or to withdraw CSF for diagnostic purposes.

Epidural injections or infusions are given into the epidural space between the Dura mater (the outermost protective membrane covering the spinal cord) and the vertebrae. This route is commonly used for spinal anesthesia, for example during childbirth.



**Figure No. 3: Intraspinal injection**

### **Intra-articular injections:**

Intra-articular injections are given into the synovial fluid of joint cavities such as the knee. Aqueous solutions or suspensions can be administered by this route. This route of injection produces a local effect, and typically anti-inflammatory drugs are administered to treat arthritic conditions or sports injuries.

### **Ophthalmic injections:**

Ophthalmic injections are administered either around or into the eye in the latter case these are referred to as intraocular injections.

Subconjunctival injections usually of 1ml or less are administered under the conjunctiva or into the skin surrounding the eye (inside the eyelid for instance).

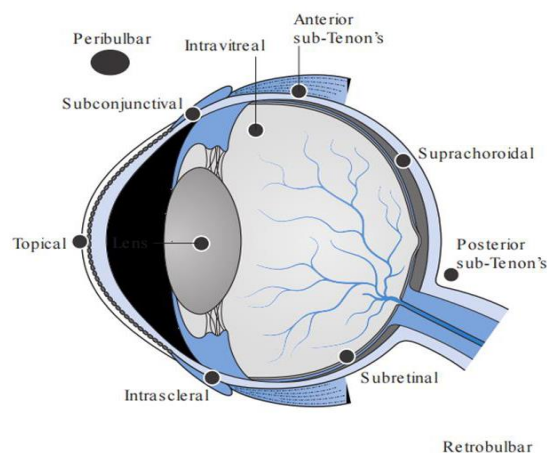
Intraocular injections can be further classified as intracameral injections into the anterior chamber of the eye (in front of the lens), or intravitreal injections into the vitreous chamber (behind the lens).

Intracameral injections can be from 0.1ml to 1ml in volume depending on whether the drug is left in the eye or administration during surgery on the open eye.

This route has been used to administer antibiotics or local anesthetics during eye surgery (e.g., cataract surgery).



Intravitreal injections are used to administer some different drugs which are used to treat various ocular diseases. Because of the danger caused by raising intraocular pressure which can damage the retina, a maximum volume of only 0.1 ml can be administered by the intravitreal route.



**Figure No. 4: Ophthalmic injections**

#### **Formula considerations of parenteral products:**

Solvents & Vehicles must meet special purity & another standard to assure safety.

Added substances (buffer, stabilizers, and preservatives) should be approved for parenteral products.

Prepared in controlled areas under strict sanitation standards & people should be specially trained, clothed to maintain sanitation.

Packing hermetically sealed containers of specific & high purity.

Volume slightly excess of the labeled size to help administration.

Volume is limited depending on route and type (single or multiple).

Dry parenteral should be reconstituted fast with (Lyophilized).

The finished products must meet sterility standards.

Must be pyrogen-free.

No particulate matter.

## Formulation of Parenterals: <sup>[14]</sup>

1 Active drug

2 Added substances

- Antimicrobial agent
- Buffer - Antioxidant
- Tonicity agent
- Chelating agent
- Complexing and surface-active agent
- Solublizers

3. Vehicle

- Aqueous
- Non-aqueous



Active drug: It is an active pharmaceutical ingredient. A thorough evaluation of the properties of the active drug or drug is essential in developing a stable and safe parenteral dosage form.

### Added substances:

*Antimicrobial agent:* Substance that kills or slows the growth of microbes. The antimicrobial agent serves to maintain the sterility of the product during its shelf life and use. They are required in preparations intended for multiple dosing from the same container because of the finite probability of accidental contamination during repeated use. They are also included, in some single-dose products to provide additional assurance of product sterility. Most commonly used parenteral antimicrobial preservative includes phenylmercuric nitrate and thiomersal 0.01%, benzethonium chloride and benzalkonium chloride, phenol or cresol 0.5%, chlorobutanol 0.5%, methylparaben, propylparaben.<sup>[15,16]</sup>

*Buffer:* Buffers are added to a formulation to adjust the pH to optimize solubility and stability. For parenteral preparations, the pH of the product should be close to physiologic

pH. The selection of buffer concentration (ionic strength) and buffer species are important. Citrate and acetate buffer, phosphate buffer.

*Antioxidant:* Salts of sulfur dioxide, including bisulfite, metabisulfite, 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 salts are added to the solution, the antioxidant moiety depends on the final concentration of the compound and the final pH of the formulation.<sup>[17]</sup>

*Tonicity agent:* Injectable solutions that are to be given intravenously must be 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 haemolysis or crenation of red blood cells. Tonicity can be measured by an osmometer and fragility point. Electrolytes: sodium chloride; Nonelectrolytes: glucose, mannitol, glycerine; Isotonic: dextrose injection 5% and sodium chloride injection 0.9%.<sup>[18]</sup>

*Chelating agent:* Only a limited number of chelating agents are used in parenteral products. They serve complex heavy metals and therefore can improve the efficacy of antioxidants or preservatives. disodium EDTA, citric acid, tartaric acid, and some amino acids also can act as chelating agents.<sup>[19]</sup>

*Complexing and surface-active agent:* Increase and maintain drug solubility. Examples include complexing agents and surface-active agents. The most commonly used complexing agents are cyclodextrins, including captisol. The most commonly used surface-active agents are polyoxyethylene Sorbitan monolaurate (tween 20) and polyoxyethylene Sorbitan monooleate (tween 80).<sup>[20]</sup>

*Solubilizers:* Solubilizers are used to enhance and maintain the aqueous solubility of poorly water-soluble drugs.<sup>[21]</sup>

*Vehicles:* Aqueous: It can be water and water-miscible liquids. Water: Most liquid injections are quite dilute, the component present in the highest proportion is the vehicle. The vehicle of the greatest importance for parenteral products is water. WFI is highly purified water used as a vehicle for injectable preparations which will be subsequently sterilized. USP requirements include not more than 10 parts per million of total solid. the pH of 5-7 WFI may be prepared

by either distillation or reverse osmosis. Stored for less than 24 hrs. at RT or for longer times at a specific temperature should meet the USP pyrogen test.<sup>[22]</sup>

*Water miscible:* Several solvents that are miscible with water have been used as a portion of the vehicle in the formulation of parenteral. These solvents are used to solubilize certain drugs in an aqueous vehicle and to reduce hydrolysis. The most important solvents in this group are ethyl alcohol, liquid polyethylene glycol, and propylene glycol. Ethyl alcohol is used in the preparation of solutions of cardiac glycosides and the glycols in solutions of barbiturates, certain alkaloids, and certain antibiotics. Such preparations are given intramuscularly. There are limitations with the amount of these co-solvents that can be administered, due to toxicity concerns, greater potential for haemolysis, and potential for drug precipitation at the site of injection.<sup>[23]</sup>

*Non-Aqueous:* The most important group of non-aqueous vehicles is the fixed oils. The oils most commonly used are corn oil, cottonseed oil, peanut oil, and sesame oil. Fixed oils are used as vehicles for certain hormones (eg., progesterone, testosterone, deoxycorticosterone) and vitamin (eg., Vitamin K, Vitamin E) preparations.<sup>[24]</sup>



**Figure No. 5: Ampoules for parenterals**

**Others included in the formulation of parenteral products:**

Crystal characteristics

Chemical modification of the drug

Polymorphism

pH and pKa

### **Crystal characteristics:**

Many dry solid parenteral products, such as the cephalosporins are prepared by sterile crystallization techniques. 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 sterile suspensions. For example, when the crystallization process for sterile ceftazidime pentahydrate was modified to increase the density and decrease the volume of the dose, the rate of dissolution increased significantly.

### **Chemical modification of the drug:**

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 other modification of the parent structure may be employed with parenteral drugs to increase stability, alter drug solubility, enhance depot action, and avoid formulation difficulties, and, possibly, decrease pain on injection. The modified drug that converts back to the active parent structure is defined as a pro-drug. This conversion usually occurs within the body system or, for some drugs that are formulated as dry powders, occurs on reconstitution. The preparation of pro-drugs is becoming a common practice with many types of drugs, example of antibiotic prodrugs includes 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 may require high solubility for the drug to be incorporated into acceptable volumes for bolus administration. Sodium and potassium salts of weak acids and hydrochloride and sulfate salts of weak bases are widely used in parenteral requiring highly soluble compounds, based on their overall safety and history of clinical acceptance.

### **Polymorphism:**

The literature lists numerous examples of polymorphism i.e., the existence of several crystal forms of a given chemical that exhibit different physical properties. The conversion of one polymorph to another may cause a significant change in the physical properties of the drug and critical quality attributes of drug products.

### **pH and pKa:**

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 compatibility of drugs with various infusion fluids.

### **Parenteral Dosage forms:**

#### **Solutions:**

Most injectable products are solutions. Solutions The simplest and most convenient form of presentation of an injectable product is an isotonic aqueous solution, which has a pH close to that of blood and body tissues (pH 7.4). Parenteral solutions include large volume parenterals (LVP), small volume parenterals (SVP), and irrigation solutions. Infusion fluids are aqueous solutions given in larger volumes than those normally administered by intravenous injection. Infusions generally include preparations used for basic nutrition, restoration of electrolyte balance, fluid replacement, etc. The formulation aspect of solutions includes vehicles and added substances. There are three types of vehicles used for the preparation of injectable solutions. One is aqueous vehicles which are officially recognized to which drug is added at the time of administration i.e. sodium chloride injection, ringer's injection, dextrose injection, lactated ringer's injection, etc. The second one is water-miscible vehicles that are used to partially dissolve the drug in combination with water i.e. cardiac glycosides solutions are prepared in ethyl alcohol and glycols are used for dissolving barbiturates but these preparations are given intramuscularly. The third and last category involves non-aqueous vehicles which are fixed oils. According to USP specifications, fixed oils should be of vegetable origin so that they can be metabolized easily in the body i.e. cottonseed oil, corn oil. Added substances in parenteral solutions may involve antimicrobial agents, buffers, chelating agents, etc.<sup>[25]</sup>

#### **Suspensions:**

Parenteral suspensions are a useful dosage form for administering insoluble or poorly soluble drugs. The drug is dispersed in the aqueous/oily solution for aqueous/oily suspensions respectively. The main property, a suspension should possess for parenteral delivery is that it should not produce tissue irritation on injection. The larger surface area of dispersing drug

ensures higher solubility which helps in providing a high degree of availability for absorption of the drug. The parenteral suspension provides more prolonged release as compared to the solution from the injection site. This system is used through the subcutaneous and intramuscular routes. Suspensions are better than solutions as they provide increase resistance to hydrolysis and oxidation as the drug is present in solid form. Despite all these benefits, many problems are associated with suspensions like difficulty in formulation, stabilization of suspensions for the period between manufacture and use, and chances of nonuniformity of dose at the time of administration.<sup>31</sup> Some of the official parenteral suspensions include sterile ampicillin suspension USP'2009, sterile aurothioglucose suspension USP'2009 - vegetable oil suspension, tetanus toxoid adsorbed USP'2009, IP'96, betamethasone acetate suspension USP'2009 aq. suspension, Insulin inc suspension USP'2009, IP'96 aq. suspension and procaine penicillin suspension IP'96 etc. The formulation aspect of suspension involves drug and added agents like wetting agents (particularly surfactant of 7-9 HLB values), buffers, viscosity-increasing agents (natural gums like tragacanth, acacia), preservatives, etc. Some workers prepared a pharmaceutical aqueous suspension formulation for parenteral administration having substantially stabilized pH, comprising a steroidal compound with an effective concentration of L-Methionine (pH controlling agent).

### **Emulsions:**

An emulsion is a two-phase system prepared by combining two immiscible liquids, one of which is dispersed uniformly throughout the other and consists of globules that have diameters equal to or greater than those of large colloidal particles.<sup>[26,27]</sup> Emulsions are generally used in the administration of total parenteral nutrition (TPN). TPN is the practice of feeding patients who are unable to get their nutrition through eating, mainly for the coma patients, etc. It is normally used during surgical recoveries. Emulsions generally fall into two categories i.e. a heterogenous system comprised of a drop of organic liquid immersed/surrounded in an aqueous solution that is known as oil in water emulsion (o/w type) and a heterogeneous system comprised of a drop of water immersed/surrounded in organic solutions that are known as water in oil emulsion (w/o type).<sup>[28]</sup> The formulation view of emulsion includes pharmaceutical oils (as mentioned in non-aqueous vehicles in solutions), pharmaceutical emulsifiers (surface-active agents, natural polymers, finely divide solids), preservatives, and antioxidants. Steps in emulsion formulation depend upon the type of formulation, whether an o/w emulsion or w/o emulsion, internal phase is selected in which

drug is mixed. In the external phase, the pharmaceutical emulsifier is added to stabilize the droplets that form during emulsification. A mixture of drug and internal phase is poured in a mixture of emulsifier and external phase with a high-pressure homogenization, to break the internal phase droplets. Emulsifier covers the whole surface to stabilize the droplet of the internal phase.<sup>[29]</sup> The major problem associated with emulsions is that these are thermodynamically unstable because of the increase in surface free energy of the system, which depends on the total surface area, and interfacial tension which increases by increasing the surface area of the system during emulsification.<sup>[30]</sup> Parenteral emulsions are administered through subcutaneous and intramuscular routes. Commercially available oily emulsions are intralipid 10%, lipofundin, and liposyn. The major focus on recent literature has been in the area of parenteral drug delivery like subcutaneous, intramuscular, intraperitoneal delivery, etc. Park et al. evaluated the potential of flurbiprofen microemulsions in parenteral delivery. The pharmacokinetic studies yield a 1.5 to 2 folds increase in half-life, area under the curve, and mean residence time of flurbiprofen from microemulsions.<sup>[31]</sup> Drugs in emulsion form provide sustained release i.e., buprenorphine emulsions. An oil-in-water buprenorphine formulation including buprenorphine and a surfactant that emulsifies the buprenorphine in oil, wherein oil concentration controls the drug release. A buprenorphine oil formulation including a buprenorphine salt suspended in pharmaceutically acceptable oil.<sup>[32]</sup>

#### **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 the addition of water before administration. The reconstituted product is usually an aqueous solution; however, occasionally it may be an aqueous solution (E.g., ampicillin trihydrate and spectinomycin hydrochloride are sterile powders that are reconstituted to form a sterile suspension).

#### **Freeze drying:**

In freeze-drying a solution is filled into vials, a special slotted stopper is partially inserted into the neck of the vial, and trays of filled vials are transferred to the freeze-dryer. The solution is frozen by the 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-drying chamber is reduced to a



pressure less than 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.

**Microspheres:** Numerous biodegradable polymers have been investigated for the preparation of microspheres as depot formulations. The application of biodegradable microspheres to deliver small molecules, proteins, and macromolecules using multiple routes of administration has been widely investigated and several products have been brought to market in the last 10–20 years. A list of marketed injectable products is shown. For peptide or protein-containing microspheres mainly three processes were studied more intensively, namely the w/o/w –technique phase separation methods and to some extent spray drying. Summarized schematic representation of all three techniques. ABA (PLGA-PEO-PLGA) block copolymer was investigated over PLG polymer by using macromolecular model compounds, such as FITC-dextran (molecular mass 4-500 kDa). The in vitro release pattern of macromolecules from ABA microspheres was influenced by the molecular mass of the solute and showed continuous release profiles above a threshold level of Ca 20 kDa whereas PLG microspheres yielded biphasic release profile independent of the molecular mass of the solute. Lupron Depot, microsphere containing the LHRH superagonist leuprorelin (leuprolide) acetate with PLGA (75/25)-14000 and PLA-15000, prepared by w/o/w emulsion-solvent evaporation method. The microsphere release drug in a zero-order fashion over 1 to 3 months after intramuscular or subcutaneous injection into animals. PLGA microsphere had been also used for delivery of glycoprotein (GP) IIb/IIIa antagonist, plasmid DNA, Interleukin-1 $\alpha$ , and prolidase enzyme. 79,80,81,82

### **Liposomes:**

In the area of injectable drug delivery systems, research into liposomes played a major role in the past few decades. Lipid complex (Abelcet, Amphoteric) and three liposomal formulations, Ambisome, Daunosome, and a stealth liposome (Doxil) had got approval for human use by regulatory agencies. These products have been developed for intravascular administration, enhancement of circulation times, and reducing toxicity by lipid encapsulation. Nowadays, encapsulation of drugs into multivesicular liposomes (Depo Foam) offers a novel approach to sustained release drug delivery. Drug into unilamellar and multilamellar liposomes, and complexation of drug with lipids, resulted in products with

better performance throughout lasting several hours to a few days after intravascular administration whereas Depo Foam® encapsulation has been resulting in sustained release lasting over several days to weeks. A sustained-release depot product (Depocyt) utilizing Depo Foam technology consists of novel multivesicular liposomes characterized by their unique structure of multiple non-concentric aqueous chambers surrounded by a network of lipid membranes. The route of administration most viable for delivery of drugs via Depo Foam formulations includes intrathecal, epidural, subcutaneous, intramuscular, intra-articular, and intraocular. Depo Foam formulations of a protein such as insulin, myelopoietin (Leridistim), and peptide such as leuprolide, enkephalin, octreotide have been developed and characterized. The data show that these formulations have high drug loading, high encapsulation efficiency, low content of free drug in the suspension, little chemical change in the drug caused by the formulation process, narrow particle size distribution, and spherical morphology. Semisolid phospholipid dispersion of vesicular morphology, so-called vesicular phospholipid gels (VPGs) is another approach in liposomal technology. A protein such as erythropoietin and peptide such as Cetrorelix was developed and in vitro evaluated by vesicular phospholipid gels.

#### **Injectable drug delivery system:**

In situ forming drug delivery systems (ISFD): Injectable in situ forming implants are classified into five categories, according to their mechanism of depot formation:

Thermoplastic pastes

In situ cross-linked systems

In situ polymer precipitation

Thermally-induced gelling system

*In-situ* solidifying organogels.

#### ***In-vitro* testing of parenteral depot formulation:**

Modified release dosage forms are typically designed to release their contents over periods of weeks, months, or even years, it becomes impractical to wait for a real-time test for batch release of the product. Therefore, accelerated methods are often developed to assist in the

batch release of the product. Accelerated tests, by their nature, (e.g. elevated temperature or use of solvents) can change not only the rate of drug release but also the mechanism of release. Consequently, care needs to be taken in selecting an accelerated release method. However, the development of an additional real-time test will still be needed if the intent is to develop an in vitro test that is predictive of in vivo product performance. Success has been reported with the use of a modified rotating paddle for suspensions, Franz cell diffusion system for gels, flow-through cell for implants, and floatable dialysis bag for microspheres or nanoparticles. An important factor to be considered while selecting apparatus is its agitation characteristics, flow rate, and choice of medium (the medium should mimic the physiological conditions of the target animal). Schultz et al were investigated an in vitro release method based on rotating dialysis cells for parenteral oil depot formulations using different model conditions and test formulations. They found release rates were dependent upon the total amount of drug available for the release process and to follow first-order kinetics<sup>96</sup>. The rotating dialysis cell model offers the advantages of reproducible results and fast distribution and dissolution processes. Commercially available Float A Lyzer dialysis tubes can also be used as an alternative in vitro model operating at much less intensive stirring conditions to assess drug release from oil solutions and suspensions as well as from biodegradable microspheres. Lars Soderberg developed a membrane-free in vitro release method named “inverted cup” for drugs in the lipid formulation. Thirteen formulations containing bupivacaine, lidocaine, and/or prilocaine in lipid vehicles of different physical properties were examined and compared with in vivo data, from nerve block and pharmacokinetics study in rats as well as in vitro release profile obtained from the “single drop” technique. It showed good agreement between both in vitro release profiles and good in-vitro-in-vivo correlations.

#### **Quality control:**

#### **Product Testing and Evaluation:**

Quality control testing and evaluation are involved primarily with incoming raw materials, the manufacturing process, and the final product. Testing of incoming raw material includes routine testing on all drugs, chemicals, and packing materials. Process controls include daily testing of water for injection (USP), the conformation of filled doses and yield, 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. Pyrogen, Clarity, and particulate analysis, and for glass-sealed ampoules, leaker testing.

**Evaluation Parameters:**<sup>[33]</sup>

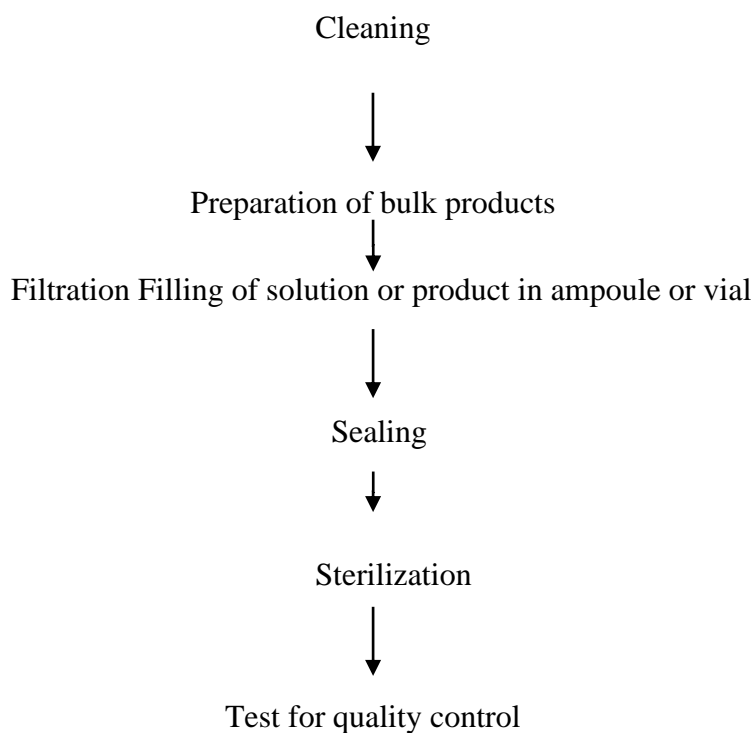
The basic quality control test which is performed on sterile parenteral products includes:

- Sterility test
- Pyrogen test
- Leaker test
- Clarity testing and particulate analysis
- Uniformity of mass
- Bacterial Endotoxin Test

**TEST FOR THE STERILITY OF THE PRODUCT:**

Sterility testing assesses whether a sterilized pharmaceutical product is free from microorganisms by counting all parts of the product through a nutrient medium. Due to the critical character of the test and the probabilities concerned in the sample only a part of a batch, it is only probable to say that no contaminating microorganisms have been found in the sample examined in the situation of the test. In other terms, it is impossible to show sterility since sampling may fail to select nonsterile containers and culture techniques that have limited sensitivity.<sup>[34]</sup>

General steps involved in parenteral preparations:



## TESTS FOR QUALITY CONTROL

### Pyrogen Test:

The presence of pyrogenic substances in parenteral preparation is determined by a qualitative biologic test which is based on the fever response of rabbits. Rabbits are used as test animals because they show a physiologic response to pyrogens similar to that of human beings. If a pyrogenic substance is injected into the vein of a rabbit, an elevation of temperature occurs within 3 hours. The specification limits and procedural details are given in the official test in the USP. The housing conditions and handling are critical to obtaining consistent results with rabbits in the test. Because of this, the use of rectal thermometers has largely been replaced by rectal thermocouples which remain in place throughout the test, eliminating the handling of the rabbits for individual temperature readings. By this method, one person can handle 100 or more animals a day as compared with about 15 by the individual thermometer method. Critical evaluations of pyrogen testing with rabbits may be found in the literature. Many medical agents, if present, interfere with the test results because of their antipyretic or other interfering effects. Therefore, the pyrogen test is performed on all vehicles used for injections, but only on those finished products that do not interfere with the test, that have a high propensity for contamination with pyrogens, or that are given in large quantities, the

considerably greater danger exists from the injection of large volume solutions containing pyrogens than from small volumes. Also, the pyrogenic effect is less with intramuscular injection than with intravenous injection.

#### **LAL Test:**

This test detects & qualifies the bacterial endotoxin that may be present in the sample using a lysate derived from the amebocytes of the horseshoe crab (*Limulus Polyphemus*).

This method utilizes the gelling property of lysate of amebocytes in the presence of pyrogen endotoxin from gram-negative bacteria within 10 minutes when incubated at 37°C.

#### **Advantages:**

5 to 10 times more sensitive than rabbit test.

Less variation & less time-consuming test.

Quantitative test.

#### **Leaker Testing:**

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 inches (64 cm) of vacuum for a minimum of 15 minutes. 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 the blue solution.

#### **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 the 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.

**Uniformity of mass:** Weight variation requirements are applied to sterile solids with or without inactive substances that have been prepared from true solution and freeze-dried in the final containers. Content uniformity requirements are applied to all cases of sterile solids that contain inactive or active substances except for special products.

**Bacterial Endotoxin test:** The bacterial endotoxin test (BET) is a test to detect or quantify endotoxins from gram-negative bacteria using Amoebocyte lysate from the horseshoe crab (*Limulus polyphemus* or *Tachypleustridentatus*).

#### **The controlled environment required for parenteral preparation:**

Clean Room Classified Areas: Due to the extremely high standards of cleanliness and purity that must be met by parenteral products, it has become standard practice to prescribe specifications for the environments (cleanrooms) in which these products are manufactured.<sup>[35]</sup>

The Critical and General area of the clean room:

The cleanroom divides into:

#### **1. Critical Area**

The critical area is the area around the point of the production where contamination can gain direct access to the process. This area is often protected by localized laminar flow clean benches and workstations.

## 2. General Area

The General area is the rest of the cleanroom where contamination will not gain direct entry into the product but should be kept clean because of the transfer of contamination into the critical area. The critical area must be cleaned most often with the best cleaning ability without introducing contamination.<sup>[36,37]</sup>

**Table No. 3: Airborne particulate classification for Grade A, B, C, and D**

Grade	The maximum permitted number of particles/m <sup>3</sup>			
	At rest		In operation	
	0.5mm	5mm	0.5mm	5mm
A	3500	0	35000	0
B	3500	0	350000	2000
C	350000	2000	3500000	20000
D	3500000	20000	Not defined	Not defined

**Table No. 4: Cleanroom classification**

FS209 Clean room Classification	ISO 14644-1 Clean room Classification	NMT 0.5µ m particles/m <sup>3</sup>	Viable Microbes (cfu/m <sup>3</sup> )	Average Airflow Velocity (fpm)	Air change/hr
100000	8	3520000	100	5 to 10	5 to 48
10000	7	35200	10	10 to 15	60 to 90
1000	6	35200	7	25 to 40	150 to 240
100	5	3520	1	40 to 80	240 to 480

### Types of Parenteral Devices:

#### Syringe:

Syringe Syringes and needles are sterile devices used to inject solutions into or withdraw secretions from the body. The syringe is a calibrated glass or plastic cylinder with a plunger at one and an opening to which the needle attaches. The word "syringe" is derived from the Greek syrinx = "tube" via back-formation of a new singular from its Greek-type plural "syringes". There are different types and sizes of syringes used for a variety of purposes.



Syringe sizes may vary from 0.25 ml to 450 ml and can be made from glass or assorted plastics.

Examples: - medical syringe, insulin syringe, disposable syringe & tuberculin syringe.

**Needle:**

Needles is a slender, sharply pointed instrument or devise used for suturing, ligaturing, or puncturing, removal of material from a clinically or radiologically identified mass by aspirating it through a hollow needle attached to a syringe. Needles are almost always disposable, but reusable ones are available for home use by a single patient. The diameter of the needle is indicated by the needle gauge. Various needle lengths are available for any given gauge. There are several systems for gauging needles, including the Stubs Needle Gauge, and the French Catheter Scale. Needles in common medical use range from 7 gauge (the largest) to 33 (the smallest) on the Stubs scale. Twenty-one-gauge needles are most commonly used for drawing blood for testing purposes, and sixteen- or seventeen-gauge needles are most commonly used for blood donation, as they are large enough to allow red blood cells to pass through the needle without rupturing (this also allows more blood to be collected in a shorter time). Larger-gauge needles (with a smaller diameter) will rupture the red blood cells, and if this occurs, the blood is useless for the patient receiving it. Although reusable needles remain useful for some scientific applications, disposable needles are far more common in medicine. Disposable needles are embedded in a plastic or aluminum hub that attaches to the syringe barrel using a press-fit or twist-on fitting.

Examples: - hypodermic needles, winged needles.

**Cannular:**

A cannula (from Latin "little reed"; plural cannulae) or cannula is a tube that can be inserted into the body, often for the delivery or removal of fluid. Cannulae normally come with a trocar attached, which allows puncturing of the body to get into the intended space. There are, however, 11 different kinds of cannulae: Bias Grind, Vet Point, Lancet Point, Deflected point (Anti-Coring), Pencil Point, Closed-End Consistent Wall, Welded "Ball" End, Bullet Point, Razor Edge, Probe Point (Blunt End), and Trocar. Intravenous cannulae are the most common in-hospital use. A variety of cannulae are used to establish cardiopulmonary bypass in cardiac surgery. The nasal cannula is a piece of plastic tubing that runs under the nose and is used to administer oxygen.

Examples: Intravenous (IV) cannulation & Nasal cannulation.

### **Catheter:**

In medicine, a catheter is a tube that can be inserted into a body cavity, duct, or vessel. Catheters thereby allow drainage, injection of fluids, or access by surgical instruments. The process of inserting a catheter is catheterization. In most uses, a catheter is a thin, flexible tube ("soft" catheter), although in some uses it is a larger, solid tube ("hard" catheter). A catheter left inside the body, either temporarily or permanently, may be referred to as an indwelling catheter. A permanently inserted catheter may be referred to as a permcath. The word "catheter" in turn came from "kathiemai" meaning "to sound" with a probe. The ancient Greeks inserted a hollow metal tube through the urethra into the bladder to empty it and the tube came to be known as a "katheter." The French catheter scale or "French units" (Fr) is commonly used to measure the outside diameter of needles, catheters, and other cylindrical medical instruments. Fr is equivalent to  $0.33 \text{ mm} = .013" = 1/77"$  of diameter. Thus, the size in French units is roughly equal to the circumference of the catheter in millimeters.

Examples: Arterial catheter, Balloon catheter, Cardiac catheterization, Central venous catheter, Dialysis.

### **Feeding Tube:**

A feeding tube is a medical device used to provide nutrition to patients who cannot obtain nutrition by swallowing. The state of being fed by a feeding tube is called enteral feeding or tube feeding. Placement may be temporary for the treatment of acute conditions or lifelong in the case of chronic disabilities. A variety of feeding tubes are used in medical practice. They are usually made of polyurethane or silicone. The diameter of a feeding tube is measured in French units (each French unit equals 0.33 millimeters). They are classified by site of insertion and intended use.

Examples: nasogastric & gastric feeding tube.

### **Stents:**

In medicine, a stent is a man-made 'tube' inserted into a natural passage/conduit in the body to prevent, or counteract, a disease-induced, localized flow constriction. The term may also refer to a tube used to temporarily hold such a natural conduit open to allow access for surgery. A stent is a wire metal mesh tube used to prop open an artery during angioplasty. The stent is

collapsed to a small diameter and put over a balloon catheter. It's then moved into the area of the blockage. When the balloon is inflated, the stent expands, locks in place, and forms a scaffold. This holds the artery open. The stent stays in the artery permanently, holds it open, improves blood flow to the heart muscle, and relieves symptoms (usually chest pain). Within a few weeks of the time the stent was placed, the inside lining of the artery (the endothelium) grows over the metal surface of the stent<sup>14</sup> Stents are used depending on certain features of the artery blockage. This includes the size of the artery and where the blockage is. Stenting is a fairly common procedure; in fact, over 70 percent of coronary angioplasty procedures also include stenting.

Examples: - drug-eluting stents.<sup>[38]</sup>

### **Parenteral therapy is used to:**

- create a localized effect.
- The oral route cannot be used for drug administration.
- Easy administration of drugs to the unconscious patient.
- Quickly accurate fluid and electrolyte imbalance.
- Accurate delivery of the drug to the target tissues.

### **Filling and sealing control of parenteral products:**

GMP practices need that in method quality assurance testing be effectively intended during all stages of manufacturing that some samples have for testing and the type of testing is dependent upon the batch size and the type of parenteral product. If the difference from particular limits occurs the essential corrective action is taken and recorded and a resample is taken and tested to find out whether the quality characteristic of the parenteral product is now inside limits in some instances as in the case of volume examination if the deviation is too much all injectables produced before the corrective action should be isolated accounted for and rejected.

### **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 compatibility and stability than do other pharmaceutical dosage forms [39] 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.



**Figure No. 6: Packaging of Parenterals**

**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 identify the drug, its concentration, handling or storage conditions, and any special precautions, the dose or concentration must be predominantly 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.

**Table No. 5: List of Marketed Formulations of Parenteral**

**Solutions**

Parenteral Solutions	Marketed Formulation
LVPs	0.9% sodium chloride injection, USP 5% sodium chloride injection 5% dextrose injection, USP 10% dextrose injection, USP Lactated ringers and 5% Ringers injection
Irrigation solutions	0.9% sodium chloride irrigation Tis- u- sol® solution pentalyte irrigation 1.5% glycine irrigation, USP

**CONCLUSION:**

Extended-release parenteral products are complex dosage forms, requiring careful development of test methods and acceptance criteria for the specifications. In particular, the *in-vitro* release test method and acceptance criteria require rigorous scientific consideration and should be developed to understand the mechanisms of drug release. Major progress in the development of parenteral sustained-release systems has been made in recent years as evidenced by the regulatory approval. The objective of a parenteral controlled drug delivery system is to achieve a desired pharmacological response in a sustained manner at a selected site without undesirable interactions at the other sites. This is especially important in cancer chemotherapy, enzyme replacement therapy. The final specifications need to ensure the safety, identity, strength, performance, and quality of the drug product at release and during storage through the end of its shelf-life. Targeted and controlled drug release is an effective approach in avoidance of hepatic first-pass metabolism, rapid onset of action, better patient compliance, enhancement of bioavailability, etc.

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## CONFLICT OF INTEREST:

The author reports no conflicts of interest.

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