INJECTABLE DRUG DEVELOPMENT

TECHNIQUES TO REDUCE PAIN AND IRRITATION

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Challenges in the Development of Injectable Products

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The injection of drugs is necessary either because a need exists for a very rapid therapeutic effect, or the drug compound is not systemically available by non-injectable routes of administration. Early use of injections led to many adverse reactions because the needs for sterility and freedom from pyrogenic contamination were poorly understood (Avis 1992). Although Pasteur and Lister recognized the need for sterilization to eliminate pathogenic microorganisms during the 1860s, sterilization technologies did not advance until much later. For example, the autoclave was discovered in 1884, membrane filtration in 1918, ethylene oxide in 1944, high efficiency particulate air (HEPA) filters in 1952, and laminar airflow in 1961. Increases in body temperature and chills in patients receiving injections were observed in 1911, which were found in 1923 to be due to bacteria-produced pyrogens. The science and technology of manufacturing and using injectable products have both come a long way since their inception in the mid-1850s. However, the assurance of sterility, particularly with injectable products manufactured by aseptic manufacturing processes, continues to be tremendously challenging to the parenteral drug industry.

Injectable products have some very special characteristics unlike any other pharmaceutical dosage form (Table 1.1). Each of these characteristics offers unique challenges in the development, manufacture, testing, and use of these products. These will be discussed more specifically in later sections of this chapter.

Table 1.1. Special Characteristics of and Requirements for Injectable Dosage Forms

- Toxicologically safe—many potential formulation additives are not sufficiently safe for injectable drug administration
- Sterile
- Free from pyrogenic (including endotoxin) contamination
- Free from foreign particulate matter
- Stable—not only physically and chemically but also microbiologically
- Compatible with intravenous admixtures if indicated
- Isotonic

General Challenges

From a formulation development standpoint, the injectable product formulation must be as simple as possible. As long as there are no major stability, compatibility, solubility, or delivery problems with the active ingredient, injectable product formulation is relatively easy to accomplish. Ideally, the formulation will contain the active ingredient and water in a vehicle (e.g., sodium chloride or dextrose) that is isotonic with bodily fluid. Unfortunately, most active ingredients to be injected do not possess these ideal properties. Many drugs are only slightly soluble or are insoluble in aqueous media. Many drugs are unstable for extended periods of time in solution and even in the solid state. Some drugs are very interactive with surfaces such as the container/closure surface, surfaces of other formulation additives, or surfaces of administration devices.

There are three interesting phenomena that make injectable drug formulation, processing and delivery so complicated compared to other pharmaceutical dosage forms:

1. There are relatively few safe and acceptable formulation additives that can be used. If the drug has significant stability, solubility, processing, contamination, and/or delivery problems, the formulation scientist does not have a plethora of formulation materials that can be used to solve these problems.

2. In non-parenteral processing, because of the frequent potential for powder toxicology concerns, the process is set up to protect personnel from the product. In injectable product processing, the opposite exists—the process is set up to protect the product from personnel because the major sources of contamination are people.

3. When a manufacturer releases a non-injectable dosage form to the marketplace, the ultimate consumer takes that dosage form from its package and consumes it. Because there is little manipulation of the non-injectable dosage form, potential problems created by the consumer of these products are infrequent. However, most injectable dosage forms experience one or several extra manipulations before administration to the patient. Injectable drug products are withdrawn from vials or ampoules, placed in administration devices, and/or combined with other solutions, and they are sometimes combined with other drugs. The point here is that something is usually done to the injectable product that can potentially affect its stability or solubility, or another performance factor; such manipulations are done beyond the control of the manufacturer. Yet when problems occur, e.g., stability or solubility issues, the manufacturer is responsible for solving them even though the manufacturer did not cause them.

Safety Concerns

Drug products administered by injection must be safe from two standpoints: (1) the nature of the formulation components of the product and (2) the anatomical/physiological effects of the drug product during and after injection.

Compared to other pharmaceutical dosage forms, there are relatively few formulation additives a formulation scientist can choose from to solve solubility and/or stability problems, maintain sterility, achieve and maintain isotonicity, extend or control the release of drugs from depot injections, or accomplish some other need from a formulation standpoint (e.g., bulking agent, viscosity agent, suspending/emulsifying agent). Because of the irreversibility of the injectable route of administration and the immediate effect and contact of the drug product with the bloodstream and systemic circulation, any substance that has potential toxic properties, either related to the type of substance or its dose, will either be unsuitable for parenteral administration or will have restrictions for the maximum amount to be in the formulation. For example, the choices of antimicrobial preservative agents for parenteral administration are very limited, and even those agents that are acceptable have limits on how much of the agent can be contained in a marketed dosage form. Similar restrictions exist for antioxidant agents, surface active agents, solubilizers, cosolvents, and other stabilizers (e.g., disodium ethylenediaminetetraacetic acid [EDTA]).

There are many potential clinical hazards that may result from the administration of drugs by injection (Duma et al. 1992) (Table 1.2). Several of these hazards (e.g., hypersensitivity reactions, particulate matter, phlebitis)

Table 1.2. Clinical Hazards of Parenteral Administration

Air emboli

- Limited to IV or IA (intra-arterial) usage

Bleeding

- Usually related to patient's condition

Fever and Toxicity

- Local or systemic
- Secondary to allergic or toxic reaction

Hypersensitivity

- Immediate and delayed

Incompatibilities

- Can be most threatening if occurring in the vascular compartment

Infiltration and extravasation

- Limited to IV or IA usage

Overdosage

- Drugs or fluids

Particulate matter

- Most serious in IV or IA administration
- Can cause foreign body reaction

Phlebitis

- Usually with IV administration

Sepsis

- May be localized, systemic, or metastatic

Thrombosis

- Limited to IV or IA administration

can be directly related to formulation and/or packaging components. For example, some well-known hypersensitivity reactions exist with the use of bisulfites, phenol, thimerosal, parabens, and latex rubber.

Microbiological and Other Contamination Challenges

There are three primary potential contamination issues to deal with. The first is to achieve and maintain *sterility*. Sterility, obviously, is the uniquely premier attribute of a sterile product. The concept of sterility is intriguing because it is an absolute attribute, i.e., the product is either sterile or not sterile. The achievement, maintenance, and testing of sterility involve challenges that occupy the time, energy, and money of thousands of people and numerous resources. Sterility, by definition, is simple—the absence of microbial life. However, how does one prove sterility? Compendial sterility tests use a very small sample from a much larger product population. How confident can one be of the sterility of each and every unit of product based on the test results of a very small sample size? Sterility essentially cannot be proved; it can only be assured. This is a huge challenge to the parenteral drug and device industry.

Sterility can be achieved by a variety of methods, including saturated steam under pressure (the autoclave), dry heat, gases such as ethylene oxide and vapor phase hydrogen peroxide, radiation such as cobalt 60 gamma radiation, and aseptic filtration through at least 0.2 μm filters. Different types of materials and products are sterilized by different methods. For example, glass containers are usually sterilized by dry heat; rubber closures and filter assemblies by saturated steam under pressure; plastic and other heat labile materials by gaseous or radiation methods; and final product solutions either by saturated steam under pressure (if the product can withstand high temperatures), or, more commonly, by aseptic filtration. Each of these sterilization procedures must undergo significant study (process validation) in order to ensure that the method is dependable to a high degree of assurance to sterilize the material/product in question under normal production conditions. Great challenges exist in performing sterilization process validation and monitoring. There are also continuous efforts to find newer or better sterilization methods to increase the convenience and assurance of sterility (Akers et al. 1997).

Injectable products must be *free from pyrogenic contamination*. Pyrogens are metabolic by-products of microbial growth and death. Pyrogenic contamination must be prevented since the most common sterilization methods (e.g., steam sterilization, aseptic filtration) cannot destroy or remove pyrogens. Prevention can occur using solutes prepared under pyrogenic conditions, pyrogen-free water produced by distillation or reverse osmosis, pyrogen-free packaging materials where glass containers have been depyrogenated by validated dry heat sterilization methods, and rubber closures and plastic materials that have been sufficiently rinsed with pyrogen-free water. The reason for Good Manufacturing Practice (GMP) requirements for time limitations during parenteral product processing is to eliminate the potential for pyrogenic contamination, since subsequent sterilization of the product will remove microbial contamination but not necessarily pyrogens.

In sufficient injected amounts, pyrogens can be very harmful to humans. Pyrogens are composed of lipopolysaccharides that will react with the hypothalamus of mammals, producing an elevation in body temperature (hence its Greek roots [*pyro* means fire and *gen* means beginning]).

Depending on the amount of pyrogen injected, other physiological problems can occur, including death. Compendial tests, both in vivo (rabbit model) and in vitro (Limulus amebocyte lysate), are established to ensure that products used in humans are tested and do not contain levels of pyrogens that will do any harm.

Injectable products, if injected or infused as solutions, must be *free from particulate matter contamination*. Particulate matter in injectables connotates at least three important perceptions:

1. The degree of product quality and the subsequent reflection of the quality of the product manufacturer.
2. The degree of product quality in the "customer's" view (patient, medical professional, regulatory agency).
3. The clinical implications of the potential hazards of particulate matter.

The first two perceptions—related to the manufacturer and to the user or customer—are relatively well-defined and understood in that evidence of particulate matter will trigger a series of reactions, ranging from product complaints to product recalls and other regulatory actions. However, the third perception, that particulate matter is clinically hazardous, begs more questions and discussion. There is substantial evidence of the adverse physiological effects of injected particulate matter, but still much conjecture regarding the relationship between the clinical hazard and the type, size, and number of particulates (Groves 1993).

Stability Challenges

Injectable drugs are administered either as solutions or as dispersed systems (suspensions, emulsions, liposomes, other microparticulate systems). The majority of injectable drugs have some kind of instability problem. Many drugs that are sufficiently stable in ready-to-use solutions have some stability restrictions such as storage in light-protected packaging systems or storage at refrigerated conditions, or there may be formulation ingredients that stabilize the drug but can themselves undergo degradation.

The *chemical stability* of injectable products generally involves two primary routes of degradation—hydrolytic and oxidative. Other, less predominant, chemical degradation mechanisms of injectable drugs involve racemization, photolysis, and some special types of chemical reactions occuring with large molecules. A majority of injectable drug products are too unstable in solution to be marketed as ready-to-use solutions. Instead, they are available as sterile solids produced by lyophilization (freeze-drying) or sterile crystallization/powder filling technologies. Drugs that can be marketed as ready-to-use solutions or suspensions still offer the challenge of needing suitable buffer systems or antioxidant formulations for long-term storage stability. Freeze-dried products can undergo degradation during the freezing and/or freeze-drying process and, therefore, require formulation additives to minimize degradation or other physical-chemical instability problems. Drugs sensitive to oxidation require not only suitable antioxidants and chelating agents in the formulation, but they also require special precautions during manufacturing (e.g., oxygen-free conditions), and special packaging and storage conditions to protect the solution from light, high temperature, and any ingress of oxygen. Stabilization of injectable drugs against chemical degradation offers a huge challenge to formulation scientists.

Physical stability problems are well-known for protein injectable dosage forms as proteins tend to self-aggregate and eventually precipitate. Many injectable drugs are poorly soluble and require cosolvents or solid additives to enhance and maintain drug solubility. However, improper storage conditions, temperature cycling, or interactions with other components of the product/package system can all contribute to incompatibilities resulting, usually, in the drug falling out of solution (manifested as haze, crystals, or precipitate). Again, the formulation scientist is challenged with finding solutions to physical instability problems. Such solutions can be found with either creative formulation techniques or special handling and storage requirements.

Microbiological issues arise with storage stability related to the container-closure system being capable of maintaining sterility of the product; the antimicrobial preservative system, if present, still meeting compendial microbial challenge tests; and the potential for inadvertent contamination of non-terminally sterilized products and the degree of assurance that such products will not become contaminated. The concern for microbiological purity as a function of product stability has caused the Food and Drug Administration (FDA) and other worldwide regulatory bodies to require manufacturers of injectable products to perform sterility tests at the end of the product shelflife or to have sufficient container-closure integrity data to ensure product sterility over the shelf life of the product.

The *compatibility* of injectable drugs when combined with one another and/or combined with intravenous fluid diluents can create significant issues for formulation scientists. Unlike solid and semisolid dosage forms, which are used as they were released from the manufacturer, injectable dosage forms are usually manipulated by people (pharmacist, nurse, physician) other than the ultimate consumer (patient) and are combined with other drug products and/or diluents before injection or infusion. These manipulations and combinations are beyond the control of the manufacturer and can potentially lead to an assortment of problems. For example, faulty aseptic techniques during manipulation (e.g., reconstitution, transfer, admixture) can lead to inadvertent contamination of the final product. In addition, drug combinations and additions to certain intravenous diluents can lead to physical and chemical incompatibilities. It is a great challenge to the injectable product formulator and Quality Control (QC) management to anticipate these potential problems and do whatever can be done to avoid or eliminate them.

Solubility Challenges

Many drugs intended for injectable administration are not readily soluble in water. Classic examples include steroids, phenytoin, diazepam, amphotericin B, and digoxin. While most insolubility problems can be solved, they usually require a great amount of effort from the formulation development scientist. If a more soluble salt form of the insoluble drug is not available (e.g., poor stability, difficulty in manufacture, cost, etc.), then two basic formulation approaches can be attempted. One involves using formulation additives such as water miscible cosolvents, complexating agents (such as cyclodextrin derivatives), and surface active agents. If none of these additives work, then the other approach involves the formulation of a more complex dosage form such as an emulsion or liposome. Table 1.3 lists the most common approaches for solving solubility problems with injectable drugs.

Table 1.3. Approaches for Increasing Solubility

Salt formation (~1000× increase)
pH adjustment
Use of cosolvents (~1000× increase)
Use of surface-active agents (~100× increase): e.g., polyoxyethylene sorbitan monooleate (0.1 to 0.5%) and polyoxyethylene-polyoxypropylene ethers (0.05 to 0.25%)
Use of complexing agents (~500× increase): e.g., β-cyclodextrins and polyvinyl pyrrolidone (PVP)
Microemulsion formulation
Liposome formulation
Mixed micelle formulation (bile salt + phospholipid)
"Heroic" measures: e.g., for cancer clinical trial formulations, use dimethylsulfoxide (DMSO), high concentrations of surfactants, polyols, alcohols, fatty acids, etc.

Packaging Challenges

A formulator can create an excellent injectable formulation that is very stable, easily manufacturable, and elegant. Yet the formulation must be compatible with a packaging system. Currently, the most common injectable packaging systems are glass vials with rubber closures and plastic vials and bottles with rubber closures. Glass-sealed ampoules are not as popular as in the past because of concerns with glass breakage and particulates. Other packaging systems include glass and plastic syringes, glass bottles, glass cartridges, and plastic bags.

The formulation scientist must recognize that rubber closures are formulations in themselves and, thus, contain several components that can either leach out of the rubber material or be responsible for adsorbing drug molecules or other components like antimicrobial preservatives from the product solution. A great amount of effort must take place to ensure that the rubber closure is compatible with the drug formulation. Studies that must be conducted include long-term stability tests, where the container is inverted so that the product experiences maximum contact with the rubber closure.

Packaging materials are known to be primary sources of particulate matter contamination due to either inadequate cleaning of the packaging material or substances leaching from the material. Examples include glass particles, polymeric particles, and rubber leachates such as zinc, aluminum, and other rubber component materials.

Manufacturing Challenges

The greatest manufacturing challenge, assuming the drug product cannot withstand terminal sterilization, is the achievement, maintenance, and assurance of sterility. Examination of a typical process flowchart in Figure 1.1 reveals many potential opportunities for contamination if the manufacturing process is not well controlled.

Table 1.4 lists all of the factors that must be in control for sterility assurance in manufacturing drug products by aseptic processing. Each of these factors requires significant resources to do the job correctly. Because of the great concerns for potential contamination of products produced by aseptic processing and the fact that the primary source of such contamination originates from people working in the aseptic environment, new technologies such as barrier isolator technology and blow-fill-seal filling systems are being developed. These technologies allow products to be manufactured aseptically in sterile environments without the need for direct contact of product and people.

Figure 1.1. Typical process flowchart.

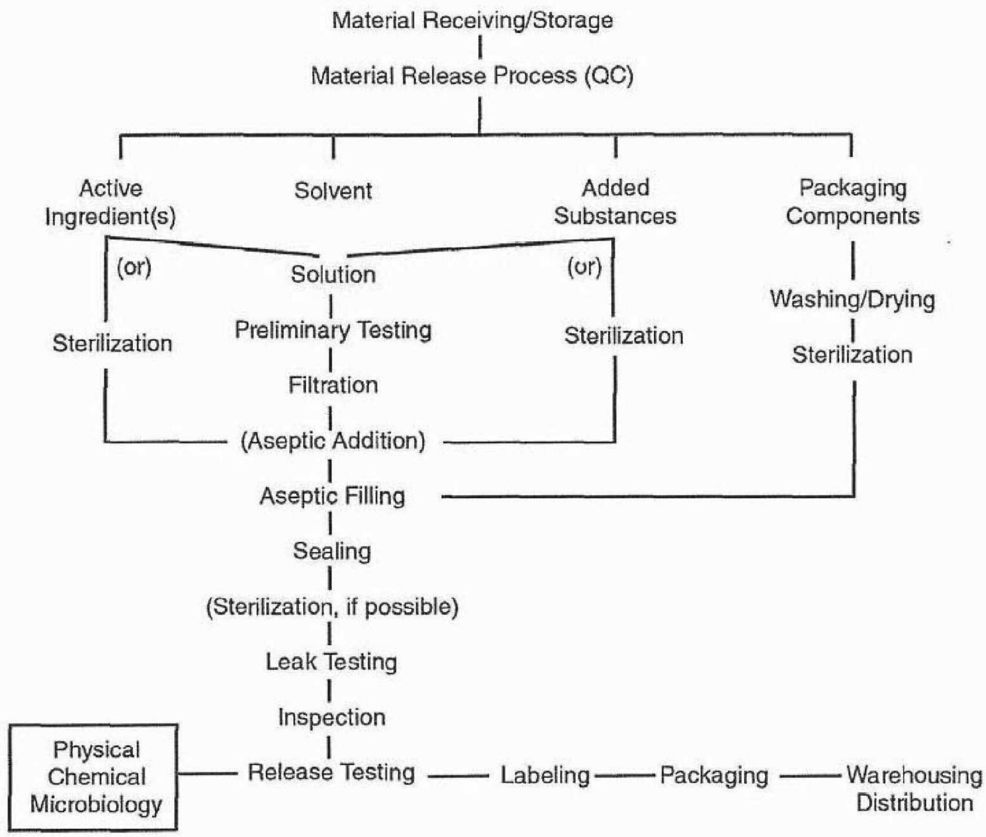

Table 1.4. Factors Involved in Sterility Assurance

Environmental monitoring	Sanitization
Operator involvement	Media fills
Facilities	Sterile filtration validation
HVAC (heating, ventilation, and air-conditioning) system monitoring and maintenance	Bioburden and microbial limits testing
Validation of sterilization cycles	Container-closure integrity
Contingency plans for unusual events during manufacturing	Adherence to and enforcement of established programs
Compendial sterility testing	Compendial preservative efficacy testing

Besides sterility assurance, other manufacturing challenges include

1. Minimizing formation of particulate matter during processing
2. Maintaining product stability, particularly of protein products, during processing
3. Special processing requirements for processing sterile powders, dispersed systems (e.g., suspensions and emulsions), and advanced formulations such as microspheres, liposomes, and devices.
4. Development, control, and validation of freeze-drying cycles
5. Sorting and labeling operations to ensure that no lot reaches the market that has significant quality defects, and that all product labels are accurate.
6. Proper handling of the finished product before release to and distribution throughout the world.

Delivery/Administration Challenges

There are many potential hazards in the administration of drugs by the injectable route. These are presented in Table 1.2. Pain and tissue irritation are caused by a variety of factors covered throughout this volume. The formulation scientist must ensure that the formulation ingredients and packaging materials are non-toxic qualitatively and quantitatively, and that the final formulation is isotonic or as close to being isotonic as possible. The challenge lies in formulating a final injectable drug product that is soluble, stable, and compatible while using a minimal number of well-known formulation additives and known packaging materials (glass, rubber, plastic). This is a challenge far easier said than done because of the severe limitations in the type and quantity of formulation additives acceptable for use in injectable products. There are, however, a number of resources available to the scientist responsible for sterile drug dosage form development that provide guidance and examples of acceptable formulation additives to solve problems with solubility, stability, maintenance of sterility, and minimization of pain and tissue irritation (Boylan et al. 1995; Akers 1995; Ahern and Manning 1992; Pearlman and Wang 1996).

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