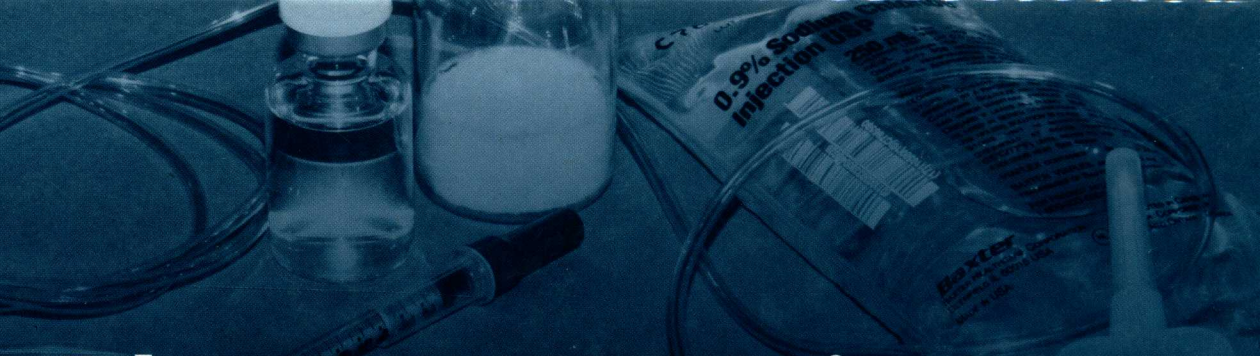

# Pharmaceutical Dosage Forms:

## Parenteral Medications

## Third Edition

### Volume 1: Formulation and Packaging

Edited by
Sandeep Nema
John D. Ludwig

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# Pharmaceutical Dosage Forms

*We dedicate this work to those who have inspired us.*
*To my parents Walter and Ruth Ludwig and my wife Sue Ludwig*
*To my parents Hari and Pratibha Nema and my wife Tina Busch-Nema*

# Foreword

I was a faculty member at the University of Tennessee and a colleague of Dr. Kenneth Avis when he conceived, organized, and edited (along with H.A. Lieberman and L. Lachman) the first edition of this book series that was published in 1984. It was so well received by the pharmaceutical science community that an expanded three-volume second edition was published in 1992. Dr. Avis did not survive long enough to oversee a third edition, and it was questionable whether a third edition would ever be published until two of his graduate students, Drs. Nema and Ludwig, took it upon themselves to carry on Dr. Avis' tradition.

Their oversight of this third edition is work that their mentor would be highly pleased and proud of. From 29 chapters in the second edition to 43 chapters in this new edition, this three-volume series comprehensively covers both the traditional subjects in parenteral science and technology as well as new and expanded subjects. For example, separate chapter topics in this edition not found in previous editions include solubility and solubilization, depot delivery systems, biophysical and biochemical characterization of peptides and proteins, container-closure integrity testing, water systems, endotoxin testing, focused chapters on different sterilization methods, risk assessment in aseptic processing, visual inspection, advances in injection devices, RNAi delivery, regulatory considerations for excipients, techniques to evaluate pain on injection, product specifications, extractables and leachables, process analytical technology, and quality by design.

The editors have done an outstanding job of convincing so many top experts in their fields to author these 43 chapters. The excellent reputations of the authors and editors of this book will guarantee superb content of each chapter. There is no other book in the world that covers the breadth and depth of parenteral science and technology better than this one. In my opinion, the editors have achieved their primary objectives—publishing a book that contains current and emerging sterile product development and manufacturing information, and maintaining the high standard of quality that readers would expect.

*Michael J. Akers*
*Baxter BioPharma Solutions*
*Bloomington, Indiana, U.S.A.*

# Preface

*Pharmaceutical Dosage Forms: Parenteral Medications* was originally published in 1984 and immediately accepted as a definitive reference in academic institutions and the pharmaceutical industry. The second edition was published in 1993. The ensuing years have produced incredible technological advancement. Classic small-molecule drugs are now complemented by complex molecules such as monoclonal antibodies, antibody fragments, aptamers, antisense, RNAi therapeutics, and DNA vaccines. There have been significant innovations in delivery devices, analytical techniques, in-silico modeling, and manufacturing and control technologies. In addition, the global regulatory environment has shifted toward greater emphasis on science-based risk assessment as evidenced by the evolving cGMPs, quality by design (QbD), process analytical technology (PAT), continuous processing, real time release, and other initiatives. The rapidly changing landscape in the parenteral field was the primary reason we undertook the challenging task of updating the three volumes. Our objectives were to (*i*) revise the text with current and emerging sterile product development and manufacturing science and (*ii*) maintain the high standard of quality the readers expect.

The third edition not only reflects enhanced content in all the chapters, but also more than half of the chapters are new underscoring the rapidly advancing technology. We have divided the volumes into logical subunits—volume 1 addresses formulation and packaging aspects; volume 2, facility design, sterilization and processing; and volume 3, regulations, validation and future directions. The authors invited to contribute chapters are established leaders with proven track records in their specialty areas. Hence, the textbook is authoritative and contains much of the collective experience gained in the (bio)pharmaceutical industry over the last two decades. *We are deeply grateful to all the authors who made this work possible.*

Volume 1 begins with a historical perspective of injectable drug therapy and common routes of administration. Formulation of small molecules and large molecules is presented in depth, including ophthalmic dosage forms. Parenteral packaging options are discussed relative to glass and plastic containers, as well as elastomeric closures. A definitive chapter is provided on container closure integrity.

Volume 2 presents chapters on facility design, cleanroom operations, and control of the environment. A chapter discussing pharmaceutical water systems is included. Key quality attributes of sterile dosage forms are discussed, including particulate matter, endotoxin, and sterility testing. The most widely used sterilization techniques as well as processing technologies are presented. Volume 2 concludes with an in-depth chapter on lyophilization.

Volume 3 focuses on regulatory requirements, risk-based process design, specifications, QbD, and extractables/leachables. In addition, we have included chapters on parenteral administration devices, siRNA delivery systems, injection site pain assessment, and control, PAT, and rapid microbiology test methods. Volume 3 concludes with a forward-looking chapter discussing the future of parenteral product manufacturing.

These three volumes differ from other textbooks in that they provide a learned review on developing parenteral dosage forms for *both* small molecules and biologics. Practical guidance is provided, in addition to theoretical aspects, for how to bring a drug candidate forward from discovery, through preclinical and clinical development, manufacturing, validation, and eventual registration.

The editors wish to thank Judy Clarkston and Lynn O'Toole-Bird (Pfizer, Inc.) for their invaluable assistance and organizational support during this project, and Sherri Niziolek and Bianca Turnbull (Informa Healthcare) for patiently leading us through the publishing process.

We also acknowledge the assistance of Pfizer, Inc. colleagues Lin Chen and Min Huang for reviewing several of the chapters.

We would like to express special gratitude to the late Kenneth E. Avis (University of Tennessee College of Pharmacy) for his dedication to teaching and sharing practical knowledge in the area of parenteral medications to so many students over the years, including us. Finally, we acknowledge the contributions of Dr Avis, Leon Lachman, and Herbert A. Lieberman who edited the earlier editions of this book series.

*Sandeep Nema*
*John D. Ludwig*

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# Contents

# 1 Parenteral dosage forms: introduction and historical perspective

John D. Ludwig

## INTRODUCTION

Parenteral dosage forms are those administered directly into body tissues rather than via the alimentary canal. "Parenteral" is derived from the Greek words *para* (beside) and *enteron* (the intestine) and most often refers to subcutaneous (SC), intramuscular (IM), or intravenous (IV) administration of drugs. Parenteral drug delivery can pose significant risk to the patient since the natural barriers of the body (gut, skin, and mucous membranes) are bypassed. The highest standards for quality and purity must be maintained throughout dosage form manufacture to protect the patient from physical, chemical, and microbial contaminants. A single contaminated vial out of a batch of thousands can seriously injure a patient (or worse). Further, if improper or poor aseptic technique is used while administering an injection the patient could be similarly harmed. The minimum quality standards for pharmaceutical manufacturers are expressed in the current good manufacturing practices (cGMPs), which are constantly evolving as technology advances. An equal burden of responsibility is placed on physicians, pharmacists, nurses, and other health professionals to follow strict good aseptic practices (GAPs) as they administer parenteral dosage forms to patients. Nosocomial infections associated with parenteral drug therapy remain a significant issue (1–4).

## ADVANTAGES AND DISADVANTAGES OF PARENTERAL DRUG DELIVERY

Parenteral drug delivery provides a number of advantages for the patient. The parenteral route provides an effective way to dose patients who are unconscious or those who cannot or would not take oral medications. A drug administered parenterally generally produces an immediate therapeutic effect and is therefore desirable in emergency situations. Parenteral administration also provides a mechanism for dosing drugs that are not bioavailable via noninjectable routes such as many protein and peptide therapeutics. Total parenteral nutrition can be provided for seriously ill patients where tube feeding is not an alternative. In addition, large amounts of fluid and electrolytes can be given relatively quickly via the IV route to patients with serious fluid loss from dehydration or gastrointestinal infections.

A significant disadvantage of injectable drug administration is that once a drug has been dosed it is difficult to reverse its effect. For example, in the event of a dosing error (overdose) with an oral tablet, gastric lavage, induced emesis, or activated charcoal can be employed. The options for reversing an IV overdose are usually very limited. Secondly, the risk of infection is always present with parenteral dosing both in the hospital/clinic setting as well as home administration. Finally, the cost per dose of parenteral drugs is typically higher than for oral medications.

## PARENTERAL DRUG DELIVERY ROUTES

Routes of parenteral drug delivery are summarized in Table 1. SC, IM, and IV are the most common modes of administration. The fastest onset of action is achieved via the IV route since the injection is directly into a vein. Relatively large amounts of fluid can be delivered quickly and efficiently using the IV route. Slower and more variable onset of action typically occurs following SC and IM administration since the drug must be absorbed into the bloodstream from the site of injection. The absorption step can be exploited for drugs requiring chronic administration. Formulations can be designed to provide sustained-release profiles therefore reducing the number of injections required and the associated risk. Examples of "depot" formulations include DEPO-PROVERA® Contraceptive Injection, which is administered deep IM every 13 weeks and depo-subQ provera 104™ which is administered SC in the anterior thigh or abdomen every 12 to 14 weeks. Intravitreal dosing has increased significantly in recent

**Table 1** Parenteral Drug Delivery Routes

| Route | Administration volume |
|---|---|
| Subcutaneous (SC) | Low, generally <2 mL |
| Intramuscular (IM) | Medium, 2 mL–5 mL |
| Intravenous (IV) | High |
| Intravitreal | Low, generally <0.1 mL |
| Intradermal (ID) | Low, 0.1 mL |
| Intra-articular | Medium |
| Intrathecal | Low |
| Intraepidural | Low |
| Intracisternal | Medium |
| Intra-arterial | High |
| Intracardiac | Medium |
| Intrapleural | Medium |
| Intraperitoneal | High |
| Intraosseous | Medium |

years because of new treatments for neovascular wet age-related macular degeneration (AMD) such as Lucentis® (ranibizumb injection) and Macugen® (pegaptanid sodium injection). The intradermal (ID) route is commonly used for very small volume injections (0.1 mL) such as the tuberculosis skin test [or tuberculin purified protein derivative (PPD) test]. Intra-articular injections directly into joint synovial fluid are routinely used to administer corticosteroids or hyaluronic acid derivatives to relieve the symptoms of osteoarthritis. Intrathecal (intraspinal) and intraepidural injections are used to deliver anesthesia, analgesics, anti-infectives, and some cancer therapies. Intracisternal administration is used to deliver critical therapeutics directly to the caudal region of the brain. Less common parenteral routes include intra-arterial, intracardiac (e.g., epinephrine for cardiac resuscitation), intrapleural, intraperitoneal, and intraosseous (bone) (5,6).

## QUALITY ATTRIBUTES OF PARENTERAL DOSAGE FORMS

Quality attributes specific to parenteral dosage forms are shown in Table 2. Injectable products must be manufactured using the highest quality active drug substance and excipients. The regulatory review process requires that each ingredient in the formulation must be justified as

**Table 2** Quality Aspects of Parenteral Dosage Forms

| Attribute | Comment |
|---|---|
| Highest level of purity for the active drug substance and excipients | Highly purified "parenteral grade" excipients are available. |
| Formulation containing the fewest number and the simplest excipients possible | The presence and amount of each excipient must be justified in regulatory filings. |
| Physical and chemical stability | Minimal degradation during shelf-life. |
| Container-closure system with low extractable/ leachable profile | Minimize the impact of the container on product purity and stability. |
| Sterile | Sterility assurance is critical for patient safety. |
| Pyrogen free | Pyrogens cause febrile response. The most potent pyrogens are bacterial endotoxins. |
| Free from visible particulate matter | Subvisible particulate matter must be excluded as much as possible as defined by compendial requirements. |
| Container-closure integrity | Product container maintains microbiological integrity during shelf-life. |
| Injection site tolerability | Formulation does not cause significant injection site irritation or tissue damage. Products are frequently formulated as isotonic solutions. |
| Detailed dosing and administration instructions including evaluation of compatibility with coadministered drugs | In clinical practice, multiple drugs are frequently administered through the same IV line to avoid the risk of an additional venipuncture. |

to why it was included and the relative amount. As a general rule, formulations with the fewest excipients and simplest composition are highly desired. The quality and robustness of the container-closure system must also be described and justified relative to extractables/leachables, container integrity (microbiological, oxygen transmission, moisture transmission), and intended clinical use. Parenteral products must be sterile, pyrogen-free, and free from visible particulate matter and remain so throughout shelf-life. Adverse injection site events are widely reported and can cause significant tissue damage. Often, the formulation can be modified to increase injection site tolerability, for example, by changing buffers and/or decreasing buffer concentration as well as rendering the dosing solution isotonic. The compatibility of the formulation should be assessed with the most likely drugs that will be coadministered with the new product. Compatibility results are generally included in the approved dosing instructions to assist pharmacists, nurses, and other health care providers.

## MILESTONES IN PARENTERAL DRUG THERAPY

Various scholars have summarized the development of parenteral drug therapy (7–13). A compiled historical timeline is presented in Table 3. The reader should be aware there is disagreement in the literature about exact dates as well as who was "first," particularly for

**Table 3** Historical Milestones in Parenteral Drug Delivery

| Year | Milestone |
|---|---|
| 1616 | William Harvey described the circulation of blood. His findings were published in 1628. |
| 1656 | Christopher Wren infused dogs with opiates and alcoholic beverages using a sharpened quill and animal bladder. |
| 1665 | Johannes Escholtz described techniques for IV infusion of drugs into humans. |
| 1796 | Edward Jenner vaccinated children against smallpox using intradermal administration with cowpox virus. |
| 1818 | James Blundell performed a successful blood transfusion following postpartum hemorrhage. |
| 1831 | William O'Shaughnessy studied the blood of cholera patients and developed the concepts for IV water and electrolyte replacement therapy. |
| 1832 | Thomas Latta established the first clinical practice of IV infusions of water and salts to treat cholera patients, based on O'Shaughnessy's work. |
| 1855 | Alexander Wood developed the first modern hypodermic syringe with a steel barrel and hollow steel needle. |
| 1867 | Joseph Lister developed the concepts of antisepsis using carbolic acid (phenol) solutions to sanitize hands, instruments, and wounds to reduce postsurgery infections. |
| 1860s–1880s | Louis Pasteur confirmed the germ theory of disease, discovered techniques for pasteurization of milk, and developed vaccinations against chicken cholera, bovine anthrax, and rabies. |
| 1879 | Charles Chamberland invented the autoclave. |
| 1884 | Charles Chamberland invented the "Chamberland filter" (porcelain) that removed bacteria from solutions prior to dosing. |
| 1891 | R.M. Matas demonstrated the effective use of IV saline solutions to treat shock. |
| 1912 | Using a rabbit model, E.C. Hort and W.J. Penfold determined the pyrogenic response following many IV injections was caused by a substance produced by gram-negative bacterial contamination of the solution (14–16). |
| 1918 | Richard Zsigmondy and W. Bachman developed technology to manufacture microporous membrane filters from cellulose esters (nitrocellulose, acetyl cellulose, cellulose acetate). |
| 1923 | Florence Siebert and L.B. Mendel developed a definitive rabbit pyrogen test model and showed that endotoxin from gram-negative bacteria was the substance responsible for the pyrogenic response following injection with sterile solutions (17–19,20). |
| 1923 | Frederick Banting and J.J.R. Macleod share the Nobel Prize in Physiology or Medicine for the extraction of insulin and demonstration of clinical efficacy. |
| 1923 | Purified insulin product marketed (Iletin®). |
| 1924 | R.M. Matas demonstrates continuous IV "drip" (21). |
| 1933 | L. Rademaker reported that after installation of a distilled water system for pharmaceutical production, pyrogenic reactions by surgery patients to parenteral injections dropped from 30% to 4% (22). |
| 1938 | Lloyd A. Hall and Carroll L. Griffith patented the use of ethylene oxide to sterilize and preserve spices. This technology was applied to sterile pharmaceutical product manufacturing during the 1940s. |

(*Continued*)

**Table 3** Historical Milestones in Parenteral Drug Delivery (*Continued*)

| Year | Milestone |
|---|---|
| 1942 | Rabbit pyrogen test (Seibert and Mendel) published in the U.S. Pharmacopeia. |
| 1940s | High Efficiency Particulate Air (HEPA) filters designed and installed for clean air supply in rudimentary cleanrooms at Manhattan project sites and biological weapons research laboratories at Fort Detrick, Maryland (10,23,24). |
| 1946 | Parenteral Drug Association founded. |
| 1950s | Cleanrooms with HEPA filtered air supply widely used for pharmaceutical fill/finish (10,23,24). |
| 1961 | Willis J. Whitfield pioneered the concept of laminar air flow and constructed the first modern cleanroom at Sandia Corporation in Albuquerque, New Mexico (10,23,24). |
| 1961 | Arvid Wretlind and O. Schuberth formulated the first lipid emulsion, Intralipid®, suitable for IV infusion (7,25). |
| 1964 | Arvid Wretlind developed a total parenteral nutrition (TPN) program providing half of the calories from lipid and half from glucose. Recognized as the father of TPN (7,25). |
| 1967 | Stanley J. Dudrick reported comprehensive technique to provide long-term total parenteral nutrition (TPN) (7,25). |
| 1969 | DW Wilmore and Stanley J Dudrick used an in-line filter to reduce the risk of IV infusions (7, 25). |
| 1971 | James F. Cooper, Jack Levin, and H.N. Wagner Jr. pioneered use of the limulus amebocyte lysate test for screening parenteral drug products for endotoxin contamination (26). |
| 1973 | Infusion Nurses Society founded. |
| 1976 | Food and Drug Administration publishes *Current Good Manufacturing Practice in the Manufacture, Processing, Packing, or Holding of Large Volume Parenterals* (never formally adopted). |
| 1978–1979 | Human insulin cloned. Human growth hormone cloned. |
| 1980s | First steps toward barrier isolator technology for aseptic fill/finish operations—gray side maintenance (24). |
| 1980s | Sterilizable isolators introduced for compendial sterility testing (27). |
| 1982 | Humulin® (human insulin recombinant) marketed. |
| 1985 | Protropin® (somatrem for injection) and Somatonorm® (somatrem) marketed. (methionyl human somatropin). |
| 1986 | Orthoclone® OTK3 marketed to treat the rejection of transplanted organs. |
| 1987 | FDA publishes *Industry Guideline on Sterile Drug Products Produced by Aseptic Processing and Guideline on General Principles of Process Validation.* |
| 1987 | Humatrope® (somatropin recombinant) and Genotropin® [somatropin (rDNA) for injection] marketed. |
| 1987 | First dual chamber pen injector launched (KabiPen®). |
| 1990s | Barrier isolator technology for fill/finish operations—Restricted Access Barrier Systems (RABS) and Isolators (24). |
| 1992 | The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is established. |
| 1994 | FDA publishes *Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products.* |
| 1996 | *Note for Guidance on Manufacture of the Finished Dosage Form* issued by the Committee For Proprietary Medicinal Products (CPMP), CPMP/QWP/486/95. |
| 1997 | First monoclonal antibody to treat cancer approved Rituxan® (rituximab). |
| 1999 | *Decision Trees for the Selection of Sterilization Methods* finalized by the CPMP, CPMP/QWP/054/98. |
| 2003 | Pharmaceutical Compounding—Sterile Preparations <797> became official in the U.S. Pharmacopeia. |
| 2003 | European Commission: Ad Hoc GMP Inspections Services Group, EC Guide to Good Manufacturing Practice Revision to Annex 1, Title: *Manufacture of Sterile Medicinal Products.* |
| 2004 | FDA publishes *Guidance for Industry Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice* (replaces 1987 version). |
| 2006 | Infusion Nurses Society publishes updated *Infusion Nursing Standards of Practice* (28). |
| 2008 | Heparin recalls due to intentional contamination during production of active pharmaceutical ingredient. |
| 2009 | European Commission: EudraLex—The Rules Governing Medicinal Products in the European Union, Volume 4, EU Guidelines to Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use, Annex 1, *Manufacture of Sterile Medicinal Products* (replaces 2003 version). |

*Abbreviation*: IV, intravenous.

discoveries prior to the 20th century. Therefore, the author attempted to arrive at reasonable dates after consulting multiple sources. It is clear early scientific findings were not disseminated quickly because of lack of modern communication tools, and scientists were often working without knowledge of similar research occurring in other laboratories. In addition, advancements were occasionally "forgotten" only to be rediscovered independently a century later, all adding to the fascinating history of medicines and health care. Specific references have been included in Table 3 for recent advances and milestones.

## CONCLUSION

The advent of safe, effective parenteral therapy has resulted in tremendous improvement in the quality of medical care around the world. Those of us fortunate enough to work in this exciting area whether in research, dosage form development, manufacturing, or clinical practice share a common goal of providing the highest standard of care. To do so requires diligence at each step in the process, be it synthesis of the active ingredient and excipients, production of the container and closure, compounding of the formulation, or aseptic fill/finish of the final product. The minimum quality standards are provided in the cGMPs, but regulatory and ethical expectations go well beyond the written requirements. Providing the highest standard of care also requires strict adherence to GAPs as the health care professional or family member is preparing and administering the dose to the patient. The risk of introducing infection and causing harm is ever present. Maxine B. Perdue of the Infusion Nurses Society summarized these sentiments as follows (29):

> "My word for competency is *excellence*. Excellence is not perfection; it is stellar performance. It is keeping current and complying with evidence-based practice standards. It is not accepting the status quo, rather, being visionary and innovative and a catalyst for research. It is sharing information with others by writing articles. . .and speaking at meetings. Each day is an opportunity to step outside the box and look at how we practice infusion therapy and to focus on each aspect of what we do as a chance to improve infusion care."

The constant pursuit of *excellence* is what drives us to the highest standard of care. Our patients deserve nothing less.

## ACKNOWLEDGMENT

The author wishes to dedicate this chapter to Kenneth E. Avis, major professor and friend, who passed away in January 1999, and to Michael J. Akers for many years of mentoring and collaboration.

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