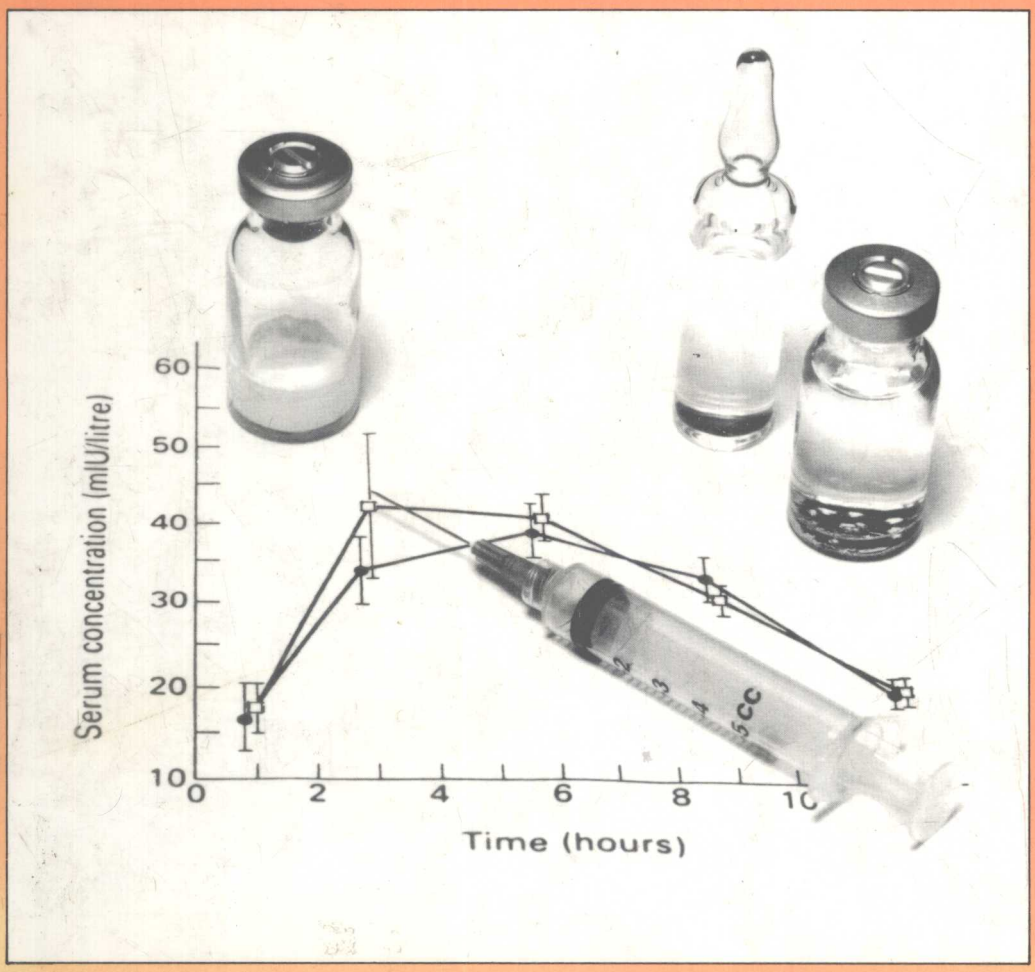
Pharmaceutical Dosage Forms:

Parenteral Medications

Volume 1

Second Edition, Revised and Expanded

Edited by Kenneth E. Avis, Herbert A. Lieberman, and Leon Lachman



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Preface

Since the publication in 1984 of the first edition of our two-volume, in-depth treatment of dosage forms for parenterals, many changes have occurred in the science and technology associated with these products. Consequently, to update and adequately cover the new subject matter devoted to parenteral medications, a three-volume set was deemed necessary. The new volumes cover topics not previously treated in the first edition; for example, genetically engineered injectable drugs and the ways in which they are prepared, sterile in vitro and in vivo diagnostic agents, the theory and practice of freeze drying, ophthalmic preparations, and validation and auditing procedures. The changes in FDA requirements for NDA and IND submissions and regulatory compliance considerations are discussed.

The topics covered in the first edition have been updated and, where necessary, expanded or rewritten, and some new authors have been added. The material in the three texts is covered with the intention of teaching both graduate and undergraduate students as well as of benefiting professionals practicing either industrial or hospital pharmacy, regulatory affairs personnel, and lawyers involved with medicinal products.

The new three-volume series is organized with the subject matter presented in three broad topical areas. Volume 1 contains chapters describing formulation and product development. Volume 2 deals with processing, and Volume 3 encompasses chapters related to quality assurance, devices, and regulatory matters. We hope this focused arrangement of subjects within each volume will facilitate and enhance the effective use of each of these books.

In Volume 1, Chapter 1, "The Parenteral Dosage Form and Its Historical Development," contains an updated version of an introduction to parenteral dosage forms and recent historical developments. Chapter 2, "Parenteral Drug Administration: Routes, Precautions, Problems, Complications, and Drug Delivery Systems," continues the thorough discussion of the administration of parenteral dosage forms, with the addition of a section on the new methods and devices for delivering drugs parenterally. Chapter 3, "Biopharmaceutics of Injectable Medications," has been expanded to include examples of biopharmaceutic/pharmacokinetic principles and to illustrate some of the variables and dynamics influencing drug absorption from parenteral sites. A new section that deals with regulatory considerations for parenteral bioequivalence is intended to provide the formulator with the basic steps required for the development of generic parenterals.

Chapter 4, "Preformulation Research of Parenteral Medications," now includes a section on the preformulation of proteins and polypeptides, a highly important topic today. These molecules are complex and can undergo physical and chemical changes markedly different from nonprotein substances. In addition, a section is included on the screening of devices used for administering drugs intravenously, since awareness is increasing that interactions between the product and the drug delivery device can result in a compromise of drug activity. Chapter 5, "Formulation of Small Volume Parenterals," includes recent work on the cyclodextrins as solubilizers as well as on the use of solubility parameters to enhance and protect solubility. Attention has been given to aluminum contamination and relevant concerns. The stability evaluation section has been revised to include updating of compendial requirements and the internationalization efforts to unify standards.

Chapter 6, "Formulation of Large Volume Parenterals," now includes an expanded discussion of the formulation of amino acid solutions and lipid emulsions. These additions allow a logical progression into a discussion of total parenteral nutrition (TPN), the solutions utilized, and additives as they affect the formulation scientist. Chapter 7, "Parenteral Products of Peptides and Proteins," is a new chapter reflecting the growing importance of these complex new drugs and their dosage forms. Various formulations of therapeutic proteins and peptides are presented, with emphasis on the stability parameters that must be evaluated and the various stabilizers that can be used to formulate a stable product. Formulation principles are illustrated with examples of recently developed protein and peptide products.

Chapter 8, "Sterile Diagnostics," is another new chapter. A general overview is given of the wide range of available diagnostic products, described by categories. This is followed by a discussion of sterile diagnostics, with an emphasis on their similarities and differences in comparison with sterile parenteral products and their processing. The preparation of human serum is elaborated as an example of a sterile diagnostic agent and its production. A final section gives a validation protocol for the aseptic filling and capping of cell culture tubes.

The next three chapters, Chapter 9, "Glass Containers for Parenterals," Chapter 10, "Use of Plastics for Parenteral Packaging," and Chapter 11, "Elastomeric Closures for Parenterals," all are extensively revised and updated. Chapter 9 introduces much more information on tubing-made containers and the controls utilized to assure their integrity of composition and physical uniformity. There is an expanded discussion of the current methods used to improve container interior-surface durability. The chapter also contains a new section on the container/closure as a system, giving the important factors necessary to insure proper functioning of these elements as an integral unit. Chapter 10 was rewritten by new authors and contains additional material on the properties of plastics and their selection for parenteral containers and other medical uses. A number of the more recent plastics, such as polysulfone and polymethylpentene, are included, and their properties are discussed. In this edition, Chapter 11 includes both thermoset and thermoplastic elastomers, some of which have the physical properties of elastomers yet offer the drug compatibility of most plastics. The new USP XXII biological tests are reviewed and the International Standards Organization (ISO) tests are fully explained and compared to the USP/NF tests used in the United States. Container/closure integrity evaluation using new test methods is also discussed.

Chapter 12, "Parenteral Products in Hospital Practice and Home Care Pharmacy Practice," has been updated and expanded to include the pharmaceutical control procedures used for parenteral products that are distributed in patient home care settings. Increased emphasis is also given to the assurance of quality in dispensing extemporaneously compounded and batch-processed sterile products.

Volume 2 contains revised chapters on the processing of small and large volume parenterals. A new chapter is included on the principles and practices in freeze drying, with formulation examples. The freeze drying process is being utilized increasingly for products that show significant instability except in the dry state, such as the new polypeptides and proteins. The chapter on the design of a parenteral production facility has been updated and a new chapter included on the distinctive characteristics of a facility for the processing of biopharmaceuticals. The chapter on personnel, their behavior requirements and their training, has been revised. Also, the chapter on controlling and monitoring the environment has been updated. The important chapter on industrial sterilization has been enlarged and updated. The final chapter is a new one concerning the formulation and development of ophthalmic preparations.

Volume 3 centers on quality assurance, devices, and regulatory matters. The first chapter is an updating of the chapter in the first edition on quality assurance. The second chapter is also a revision of the first-edition chapter dealing with records and reports. Particulate matter and its importance in parenterals is presented in the third chapter. A new chapter is introduced on validation principles and current philosophies in the manufacture of parenteral products. The chapter on federal regulations of parenterals has been updated. A new chapter is included on the audit process offering extensive insight into this highly important quality assurance procedure. The last three chapters in Volume 3 provide revised descriptions of devices, their design and manufacture, quality assurance, and GMP considerations.

As is evident from the content of these three volumes, the editors have attempted to broadly cover the subject matter concerned with parenteral medications by revising, updating, and adding new subject matter. Also, the editors strived to have each chapter be of comparable high quality in content and style, the first requirement for acceptance being that each chapter teach by clearly presenting the assigned subject.

The editors commend the resourcefulness and perseverence of the contributors to this volume for their efforts in completing their chapters despite the continued pressures placed on them by their regular jobs and other responsibilities. Each contributor, an expert in the field of the chosen topic, provides the readers with a strong technical basis to increase their understanding and broaden their knowledge in the chapter's subject matter. The editors are highly appreciative for the outstanding contributions by all of the authors.

Both the contributors and editors hope that this first volume of the three-volume set will provide essential knowledge and insight into the formulation and product development aspects of parenteral products. Further, the contributors and editors have aimed to provide a medium that will be helpful in solving problems involved with developing and maintaining superior parenteral medications.

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Contents of Pharmaceutical Dosage Forms: Parenteral Medications, Second Edition, Revised and Expanded, Volumes 2 and 3

edited by Kenneth E. Avis, Herbert A. Lieberman, and Leon Lachman

VOLUME 2

VOLUME 3

Contents of Pharmaceutical Dosage Forms: Tablets, Second Edition, Revised and Expanded, Volumes 1–3

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VOLUME 1

VOLUME 2

VOLUME 3

Contents of Pharmaceutical Dosage Forms: Disperse Systems, Volumes 1 and 2

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