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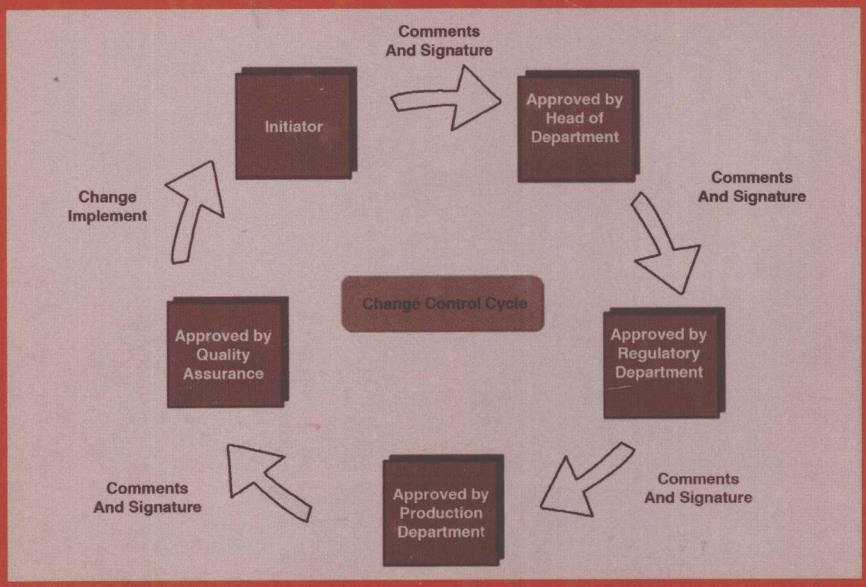
Pharmaceutical Manufacturing Handbook

Regulations and Quality



Edited by

Shayne Cox Gad

PHARMACEUTICAL MANUFACTURING HANDBOOK

Regulations and Quality

SHAYNE COX GAD, PH.D., D.A.B.T.
Gad Consulting Services
Cary, North Carolina

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CONTRIBUTORS

Emmanuel O. Akala, Department of Pharmaceutical Sciences, School of Pharmacy, Howard University, Washington, DC, *Effect of Packaging on Stability of Drugs and Drug Products*

Giuseppe Alibrandi, Università di Messina, Messina, Italy, *Alternative Accelerated Methods for Studying Drug Stability: Variable-Parameter Kinetics*

Edward R. Arling, Amgen, Inc., Thousand Oaks, California, *Creating and Managing a Quality Management System*

Christina Bartmann, Medical University of Graz, Graz, Austria, *GMP-Compliant Propagation of Human Multipotent Mesenchymal Stromal Cells*

James M. Barquest, Ground Zero Pharmaceuticals, Inc., Irvine, California, *Role of Quality Systems and Audits in Pharmaceutical Manufacturing Environment*

Denise Bohrer, Chemistry Department, Universidade Federal de Santa Maria, Santa Maria, Brazil, *Origin of Contamination*

Chung Chow Chan, Azopharma Contract Pharmaceutical Services, Miramar, Florida, *Analytical Method Validation: Principles and Practices*

Robert P. Cogdill, Duquense University Center for Pharmaceutical Technology, Pittsburgh, Pennsylvania, *Case for Process Analytical Technology: Regulatory and Industrial Perspectives*

Marc De Loose, Institute for Agricultural and Fisheries Research (ILVO), Scientific Institute for the Flemish Community, Merelbeke, Belgium, *Analytical Method Validation and Quality Assurance*

Katherine V. Domenick, Training and Communications Group, Inc., Berwyn, Pennsylvania, *Personnel Training in Pharmaceutical Manufacturing*

Michelle E. Dowling, Amgen, Inc., Thousand Oaks, California, *Creating and Managing a Quality Management System*

L. Antonio Estévez, University of Puerto Rico, Mayagüez, Puerto Rico, *Drug Stability*

D.C. Ferreira, Faculty of Pharmacy, University of Porto, Porto, Portugal, *Pharmaceutical Manufacturing Validation Principles*

Alvin Fox, University of South Carolina, Columbia, South Carolina, *Quantitation of Markers for Gram-Negative and Gram-Positive Endotoxins in Work Environment and as Contaminants in Pharmaceutical Products Using Gas Chromatography–Tandem Mass Spectrometry*

Paul A. Frankel, Amgen, Inc., Thousand Oaks, California, *Creating and Managing a Quality Management System*

David A. Gallup, Training and Communications Group, Inc., Berwyn, Pennsylvania, *Personnel Training in Pharmaceutical Manufacturing*

Srinivas Ganta, University of Auckland, Auckland, New Zealand, *Scale-Up and Postapproval Changes (SUPAC) Regulations*

Sanjay Garg, University of Auckland, Auckland, New Zealand, *Scale-Up and Postapproval Changes (SUPAC) Regulations*

Marge Gillis, Training and Communications Group, Inc., Berwyn, Pennsylvania, *Personnel Training in Pharmaceutical Manufacturing*

James R. Harris, James Harris Associates, Inc., Durham, North Carolina, *Good Manufacturing Practices (GMP) and Related FDA Guidelines*

Ashley John, New Jersey Institute of Technology, Newark, New Jersey, *Analytical and Computational Methods and Examples for Designing and Controlling Total Quality Management Pharmaceutical Manufacturing Systems*

Herman Lam, Wild Crane Horizon, Inc., Scarborough, Ontario, Canada, *Validation of Laboratory Instruments*

Marko Närhi, Helsinki University of Technology, Helsinki, Finland, *National GMP Regulations and Codes and International GMP Guides and Guidelines: Correspondences and Differences*

Kenneth J. Nolan, Nolan & Auerbach, Fort Lauderdale, Florida, *Enforcement of Good Manufacturing Practices*

Katrina Nordström, Helsinki University of Technology, Helsinki, Finland, *National GMP Regulations and Codes and International GMP Guides and Guidelines: Correspondences and Differences*

Nazario D. Ramirez-Beltran, University of Puerto Rico, Mayagüez, Puerto Rico, *Drug Stability*

Gregory N. Ranky, Public Research University of New Jersey, Newark, New Jersey, *Analytical and Computational Methods and Examples for Designing and Controlling Total Quality Management Pharmaceutical Manufacturing Systems*

Paul G. Ranky, New Jersey Institute of Technology, Newark, New Jersey, *Analytical and Computational Methods and Examples for Designing and Controlling Total Quality Management Pharmaceutical Manufacturing Systems*

Richard G. Ranky, New Jersey Institute of Technology, Newark, New Jersey, *Analytical and Computational Methods and Examples for Designing and Controlling Total Quality Management Pharmaceutical Manufacturing Systems*

Andreas Reinisch, Medical University of Graz, Graz, Austria, *GMP-Compliant Propagation of Human Multipotent Mesenchymal Stromal Cells*

Harry Rodriguez, Cordis LLC, a Johnson & Johnson Company, San Juan, Puerto Rico, *Drug Stability*

Yves Roggo, F. Hoffmann-La Roche, Ltd., Basel, Switzerland, *Process Analytical Technology; Chemical Imaging and Chemometrics: Useful Tools for Process Analytical Technology*

Eva Rohde, Medical University of Graz, Graz, Austria, *GMP-Compliant Propagation of Human Multipotent Mesenchymal Stromal Cells*

B. Saramento, Faculty of Pharmacy, University of Porto, Porto, Portugal, *Pharmaceutical Manufacturing Validation Principles*

Katharina Schallmoser, Medical University of Graz, Graz, Austria, *GMP-Compliant Propagation of Human Multipotent Mesenchymal Stromal Cells*

Puneet Sharma, University of Auckland, Auckland, New Zealand, *Scale-Up and Postapproval Changes (SUPAC) Regulations*

Evan B. Siegel, Ground Zero Pharmaceuticals, Inc., Irvine, California, *Role of Quality Systems and Audits in Pharmaceutical Manufacturing Environment*

E.B. Souto, Free University of Berlin, Berlin, Germany; Faculty of Pharmacy, University of Porto, Porto, Portugal, *Pharmaceutical Manufacturing Validation Principles*

Dirk Strunk, Medical University of Graz, Graz, Austria, *GMP-Compliant Propagation of Human Multipotent Mesenchymal Stromal Cells*

Michel Ulmschneider, F. Hoffman-La Roche, Ltd., Basel, Switzerland, *Process Analytical Technology; Chemical Imaging and Chemometrics: Useful Tools for Process Analytical Technology*

Isabel Taverniers, Institute for Agricultural and Fisheries Research (ILVO), Scientific Institute for the Flemish Community, Merelbeke, Belgium, *Analytical Method Validation and Quality Assurance*

Erik Van Bockstaele, Institute for Agricultural and Fisheries Research (ILVO), Scientific Institute for the Flemish Community, Merelbeke, Belgium, *Analytical Method Validation and Quality Assurance*

T. Vasconcelos, Laboratory of Pharmaceutical Development, BIAL, Mamede do Coronado, Portugal; Faculty of Pharmacy, University of Porto, Porto, Portugal, *Pharmaceutical Manufacturing Validation Principles*

Ranga Velagaleti, BASF Corporation, Florham Park, New Jersey, *Microbiology of Nonsterile Pharmaceutical Manufacturing; Stability and Shelf Life of Pharmaceutical Products*

Andrew A. Webster, McWhorter School of Pharmacy, Birmingham, Alabama, *Pharmaceutical Product Stability*

Jyh-hone Wang, University of Rhode Island, Kingston, Rhode Island, *Quality Process Improvement*

PREFACE

This *Handbook of Manufacturing: Regulations and Quality* focuses on all regulatory aspects and requirements that govern how drugs are produced for evaluation (and, later, sale to and use in) humans. The coverage ranges from what the issues are at the early stages (when the amounts are small and the materials of limited sophistication) up to until the issue is reproducibly and continuously making large volumes of a highly sophisticated manufactured product. These 25 chapters cover the full range from preformulation of a product (the early exploratory work that allows us to understand how to formulate and deliver the drug) to identification of sources of contamination and assessment of stability.

The *Handbook of Manufacturing: Regulations and Quality* seeks to cover the entire range of available approaches to satisfying the wide range of regulatory requirements for making a highly defined product that constitutes a successful new drug and how to do so in as effective and as efficient a manner as possible.

Thanks to the persistent efforts of Michael Leventhal, these 25 chapters, which are written by leading practitioners in each of these areas, provide coverage of the primary approaches to the fundamental regulatory challenges that must be overcome to manufacture successfully a deliverable and stable new drug.

CONTENTS

SECTION 1

GOOD MANUFACTURING PRACTICES (GMP) AND OTHER FDA GUIDELINES

1.1

GOOD MANUFACTURING PRACTICES (GMP) AND RELATED FDA GUIDELINES

JAMES R. HARRIS

James Harris Associates, Inc., Durham, North Carolina

Contents

Pharmaceutical Manufacturing Handbook: Regulations and Quality, edited by Shayne Cox Gad

1.1.1 FDA REGULATIONS: REAL AND IMAGINED

A regulation is a law. In the United States, all federal laws have been arranged or codified in a manner that makes it easier to find a specific law. The *Code of Federal Regulations* (CFR) is a compilation of all federal laws published in the *Federal Register* by the executive departments and agencies of the federal government. This code is divided into 50 titles which represent broad areas of federal regulation. Each title is further divided into chapters. The chapters are then subdivided into parts covering specific regulatory areas. Changes and additions are first published in the *Federal Register*. Both the coded law and the *Federal Register* must be used to determine the latest version of any rule. All food- and drug-related laws are contained in Title 21 of the CFR. Each title of the CFR is updated annually. Title 21 is updated as of April 1 of each year.

Because virtually all of the drug regulations are written to state what should be done but do not tell how to do it, the Food and Drug Administration (FDA) also publishes guidance documents. These documents are intended to provide precisely what the name implies—guidance. In this context, *guidance documents are not law and do not bind the FDA or the public*. Manufacturers are not required to use the techniques or approaches appearing in the guidance document. In fact, FDA representatives have repeatedly stated that the regulations were not written to suggest how something should be done in order to encourage innovation. While following the recommendations contained in the guidance documents will probably assure acceptance (agency philosophy and interpretation may have changed since the guidance document was published), other approaches are encouraged. No matter how they choose to proceed, manufacturers should be prepared to show that their methods achieve the desired results.

A method used by the FDA to "float" new ideas is to discuss them at industry gatherings such as FDA-sponsored seminars or meetings of industry groups such as the Pharmaceutical Manufacturers Association (PMA), the Parenteral Drug Association (PDA), and the International Society of Pharmaceutical Engineering (ISPE). Again, it must be remembered that while these comments reflect current FDA thinking, they are simply thoughts and recommendations. They are not law.

Several industry groups also publish comments, guidelines, and so on, that put forth current thinking of the group writing the document. These publications are interesting and often bring out valuable information. However, it is important to remember that *these publications are not regulations or even official guidance documents.* If a firm chooses to follow the recommendations of such documents, they are probably following good advice. However, since the advice comes from a nonofficial source, firms should still be prepared to defend their actions with good scientific reasoning.

1.1.2 21 CFR 210 AND 211: CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED PHARMACEUTICALS

Parts 210 and 211 of CFR Title 21 are the laws defining good manufacturing practices for finished pharmaceutical products. All manufacturers must follow these regulations in order to market their products in the United States. When a firm files an application to market a product in the United States through a New Drug Application (NDA), abbreviated NDA, (ANDA), Biological License Application (BLA),

or other product application, one of the last steps in approving the application is a preapproval inspection of the manufacturing facility. A major purpose of this inspection is to assure adherence to the GMP regulations. Preapproval inspections are a part of every application approval. Thus, if a firm has 10 applications pending, it should expect 10 inspections. The fact that the manufacturing facility has already been inspected will not alter the need for another inspection.

The FDA also has the right to visit and inspect any manufacturing facility that produces a product or products sold in the United States. Such inspections are unannounced. A manufacturer must admit an inspector when he or she appears at that facility and must do so without undue delay.

GMP requirements for manufacturers of pharmaceutical dosage forms are discussed below. This information should not be considered to be an exact statement of the law. We have attempted to show intent and, occasionally, add some comments that will clarify how that particular regulation is interpreted. For precise wording of a regulation, refer to the CFR and then check the *Federal Register* to determine if there have been any changes since the last update.

General Provisions

1. This section pertains to the manufacture of drug products for humans or animals.
2. These requirements will not be enforced for over-the-counter (OTC) drug products if the products and all their ingredients are ordinarily marketed and considered as human foods and which products may also fall within the legal definition of drugs by virtue of their intended use.

Organization and Personnel

1. Responsibilities of quality control unit
   (a) A quality control unit *must* be a part of the facility organization.
   (b) This unit must be given responsibility and authority to approve or reject all components, drug product containers, closures, process materials, packaging material, labeling, and drug products, and the authority to review production records.
   (c) Adequate laboratory facilities for testing and approval or rejection of the above listed materials must be available.
   (d) The quality control unit is responsible for approving or rejecting all procedures or specifications that impact on the identity, strength, quality, and purity of the drug product.
   (e) Responsibilities and procedures applicable to the quality control unit must be written and these procedures must be followed.
2. Personnel qualifications
   (a) Every person involved in the manufacture, processing, packing, or holding of a drug product must have education, training, and experience that enable that individual to perform their duties. Employees must be trained in the particular operations that they perform and in Current GMPs (CGMPs). The GMP training must be conducted by qualified individuals and with sufficient frequency to assure that workers remain familiar with the requirements applicable to them.

(b) Persons responsible for supervision must have the education, training, and experience to perform their assigned functions in such a manner as to assure that the drug product has the safety, identity, strength, quality, and potency that it is represented to possess.
(c) There must be an adequate number of qualified personnel to perform the needed tasks.

3. Personnel responsibilities
   (a) Personnel shall wear clean clothing appropriate for the duties they perform. Protective apparel must be worn as necessary.
   (b) Personnel shall practice good sanitation and health habits.
   (c) Only personnel authorized by supervisory personnel shall enter those areas designated as limited-access areas.
   (d) Any worker considered to have an apparent illness or open lesions that may adversely affect safety or quality of drug products shall be excluded from direct contact with product, components, or containers.
4. Consultants that advise on the manufacture, processing, packing, or holding of drug products must have sufficient education, training, and experience to advise on the subject for which they are retained. The manufacturer must maintain records of name, address, and qualifications of any consultants and the type of service they provide.

Buildings and Facilities

1. Design and construction features
   (a) Buildings should be of suitable size, construction location to facilitate cleaning, maintenance, and proper operations.
   (b) Space should be adequate for the orderly placement of equipment and materials to prevent mix-ups between different components, drug product containers and closures, labeling, in-process materials, or drug products and to prevent contamination.
   (c) The movement of components and product through the building must be designed to prevent contamination.
   (d) Operations should be performed within specifically defined areas having adequate control systems to prevent contamination or mix-ups during each of the following procedures:
      (i) Receipt, identification, storage, and withholding from use of components, drug product containers, closures, and labeling, pending the appropriate sampling, testing, and release for manufacturing or packaging.
      (ii) Holding rejected materials listed in (a) above.
      (iii) Storage of released components, drug product containers, closures, and labeling.
      (iv) Storage of in-process materials.
      (v) Manufacturing and processing operations.
      (vi) Packaging and labeling operations.
      (vii) Quarantine storage before release of drug products.
      (viii) Storage of drug products after release.
      (ix) Control and laboratory operations.