DRUGS AND THE PHARMACEUTICAL SCIENCES

GOOD MANUFACTURING PRACTICES FOR PHARMACEUTICALS

Seventh Edition

Edited by

Graham P. Bunn

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Good Manufacturing Practices for Pharmaceuticals

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Preface

This book is dedicated to my dad, Roy Bernard Bunn, of Wymondham, Norfolk, England. Without his encouragement to "Do what you love and love what you do," I would not be writing chapters in this book today. Pharmacy, medicines, quality, and most of all patient focus have been my entire career, and I would not change anything.

There have been many changes in the world of pharmacy since I started making medicinal products in the Norfolk and Norwich hospital pharmacy during the early 1970s. The changes include advances in pharmacology, discovery of new treatments, and changes in manufacturing processes technologies, with significant increase supporting documentation requirements.

Building on the vast information and reputation of original authors and further developed in the 6th edition edited by Joe Nally, I have taken the opportunity to reorganize this 7th edition to collate the related regulation parts. In addition to the core regulatory chapters, I have added new related chapters (Chapters 3, 19, 23, and 24) to provide readers with additional insight and supporting information. These new chapters include the current regulatory focus for Management Responsibility and Control, Microbiological Aspects of Pharmaceutical Aseptic Processing in the Compounding Pharmacy, Worldwide Good Manufacturing Practices, and Data Integrity and Fundamental Responsibilities. In addition, FDA regulatory inspections and enforcements have been refocused into three new chapters by the contributions from Alson and Bird LLP, Washington Attorneys.

I am privileged to have worked with many distinguished colleagues with outstanding expertise and experience in pharmaceuticals, quality, and regulatory compliance. My special thanks goes to the authors for their time and contributions to this book from over 360 years of experience and making this an exceptional 7th edition. Thank you; I am forever in your debt.

From the FDA website:

A drug is defined as:

- A substance recognized by an official pharmacopoeia or formulary.
- A substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease.
- A substance (other than food) intended to affect the structure or any function of the body.
- A substance intended for use as a component of a medicine but not a device or a component, part or accessory of a device.
- Biological products are included within this definition and are generally covered by the same laws and regulations, but differences exist regarding their manufacturing processes (chemical process versus biological process).

And as noted in Sec. 210.1, "Status of current good manufacturing practice regulations":

(a) The regulations set forth in this part and in parts 211, 225, and 226 of this chapter contain the minimum current good manufacturing practice for methods to be used in, and the facilities or controls to be used for, the manufacture, processing, packing, or holding of a drug to assure that such drug meets the requirements of the act as to *safety*, and has the *identity* and *strength* and meets the *quality* and *purity* characteristics that it purports or is represented to possess.

(b) The failure to comply with any regulation set forth in this part and in parts 211, 225, and 226 of this chapter in the manufacture, processing, packing, or holding of a drug shall render such drug to be adulterated under section 501(a)(2)(B) of the act and such drug, as well as the person who is responsible for the failure to comply, shall be subject to regulatory action.

Objectives of the pharmaceutical business include producing drugs for patients and use by healthcare professionals meeting broad requirements in a global competitive market place while keeping up with regulatory requirements and interpretations. The consequences for not being in adequate compliance can be far-reaching regulatory actions.

This business is challenging from a science and technology approach, and compliance with ever-evolving regulations adds additional complexity. No one has ever said that this business had an easy job to comply with requirements, but then that's what continuously challenges us every day.

As mentioned in the 6th edition of this book by Joe Nally (editor), and again here, pharmaceutical current good manufacturing practice (CGMP) compliance will never slow up its pace of evolution, as there are always external influences to challenge the industry. The FDA continues to evolve and develop its approach to regulating manufacturers, regulatory requirements and global harmonization of quality standards. Technological advancements do not wait for the industry but as a supporting business continue to provide new opportunities for the enhancement of regulatory compliance. The FDA evaluates these advancements for compliance with regulatory requirements and periodically issues further clarification through "Guidance for Industry" documents. Readers are encouraged to register for updates to existing and new documents from the FDA website. As noted in "Guidance for Industry 'Emerging Technology Applications for Pharmaceutical Innovation and Modernization' September 2017": "FDA continues to support flexible approaches in the manufacturing of quality pharmaceutical products. While the implementation of emerging technology is critical to advancing product design, modernizing pharmaceutical manufacturing, and improving quality, FDA also recognizes that the adoption of innovative approaches may represent challenges to industry and the Agency."

Changes in the sourcing of materials, especially active pharmaceutical ingredients and finished products to overseas companies and/or subsidiaries in other countries continues to increase the need for FDA inspections worldwide. The Government Accountability Agency noted in the December 2016 report to the Committee on Energy and Commerce, "Drug Safety: FDA Has Improved Its Foreign Drug Inspection Program, but Needs to Assess the Effectiveness and Staffing of Its Foreign Offices":

a. Globalization has complicated FDA's oversight of drugs marketed in the United States. FDA reports that more than 40% of finished drugs and 80% of active pharmaceutical ingredients are produced overseas. FDA inspects drug manufacturing establishments to ensure that the safety and quality of drugs are not jeopardized by poor manufacturing practices. Beginning in 2008, FDA established foreign offices to obtain better information on products coming from overseas and perform inspections, among other things.
b. The number of foreign inspections has consistently increased each year since fiscal year 2009. Beginning in fiscal year 2015, FDA conducted more foreign than domestic inspections. FDA has also improved the accuracy and completeness of information on its catalog of drug establishments subject to inspection. It has also reduced its catalog of drug establishments with no inspection history to 33% of foreign establishments, compared to 64% in 2010. However, the number of such establishments remains large, at almost 1,000 of the approximately 3,000 foreign establishments. FDA plans to inspect all of these establishments over the next 3 years.

On August 23, 2017, a milestone agreement was reached between the FDA, European Commission, and European Medicines Agency as noted below from the EMA website:

> The European Commission (EC), the United States (US) Food and Drug Administration (FDA), and the European Medicines Agency (EMA) have signed a new confidentiality commitment that allows the US regulator to share non-public and commercially confidential information, including trade secret information relating to medicine inspections with EU regulators. This confidentiality commitment is a

> milestone in the ongoing implementation of the mutual recognition of inspections of medicine manufacturers, and it aims to strengthen the EU-US relationship. Ultimately it will contribute to a more efficient use of inspection resources by regulators for the protection of human and animal health.
>
> The EU and the US have had confidentiality arrangements in place since 2003, allowing for the exchange of confidential information as part of their regulatory and scientific processes. However, complete exchange of information was not possible under these arrangements.
>
> The new confidentiality commitment formally recognises that FDA's EU counterparts have the authority and demonstrated ability to protect the relevant information. This step now allows the sharing of full inspection reports, allowing regulators to make decisions based on findings in each other's inspection reports and to make better use of their inspection resources to focus on manufacturing sites of higher risk.

The most significant FDA regulatory action focus areas since the last edition of this book have been in data integrity, aseptic technique, and those relating to compounding pharmacies. Data integrity is covered in a new chapter (Chapter 24, "Data Integrity and Fundamental Responsibilities") with unique perspectives contributed by two leading experts. The other two focus areas are linked, but consistent compliance requirements for aseptic technique continues to be a significant challenge for pharmaceutical companies and major pharma and relates to the significant reliance on operators (see Chapter 4, "Organization and Personnel"). A new chapter (Chapter 19, "Microbiological Aspects of Pharmaceutical Aseptic Processing in the Compounding Pharmacy") was identified and contributed by a leading microbiologist with extensive experience in this area and in the remediation of these regulatory actions.

Data integrity is not new, the basis of which are in the daily-use standard operating procedure (SOP) of every regulated business submitting data and information to FDA for application approval. Advances in technology created a need for the regulations defined in 21 CFR 211, Electronic Records; Electronic Signatures, initially made official March 20, 1997. The FDA and other regulatory agencies detected further data integrity issues leading to the issuance of the draft Guidance for Industry, "Data Integrity and Compliance with CGMP" in April 2016 and together with worldwide regulatory agencies have continued to develop the regulatory requirements and expectations through ongoing assessments.

With reference to compounding pharmacies: FDA reported on its website that "In October 2012, the United States faced the most serious outbreak associated with contaminated compounded drugs in recent history. A pharmacy in Massachusetts shipped compounded drugs that were contaminated with a fungus throughout the country, and these drugs were injected into patients' spines and joints. More than 750 people in 20 states developed fungal infections, and more than 60 people died. Approximately 14,000 patients received injections from the lots of contaminated drug product." See 2012 "Fungal Meningitis Outbreak: Persons with Fungal Infections Linked to Steroid Injections, by State, Centers for Disease Control and Prevention" for more information. As a result, on November 27, 2013, the Drug Quality and Security Act (DQSA) was signed into law. Title 1 of the new law, the Compounding Quality Act, requires compliance of compounding pharmacies with CGMPs, Section 501(a)(2)(B).

I have retained with due reference some of the wording used in the 6th edition of this book by Joe Nally because it still holds true today 40 years after its inception:

> …since 1978 the discussions, arguments and debates continue over mainly the intent and "how to" of GMP compliance. This all goes back to the original 1978 regulations and the intent of Congress. They intended that the agency (FDA) determine what constitutes current or the "C" in CGMP, based on their experience. The Congress also interpreted current as not necessarily widely prevalent. They did not require that a majority of manufacturers had to be following a practice before it was accepted as current. If a practice was shown to be feasible and valuable in assuring drug quality it could be considered current. This is what makes life in Pharmaceutical operations and CGMP compliance interesting.

For those professionals considering pharmaceuticals as a career, take a good look because it offers countless opportunities to develop and apply your creative thoughts, skills, and expertise. When you think you know it all, there is always more to do and learn as science combines with evolving regulatory compliance requirements. You will be challenged by "What if…?" and "How do you know…?" and that's what is on many minds at the end of the day and drives us getting up each morning, as each day has more challenges and problems to be solved.

The industry will continue to need people, good people, those who are passionate about what they do and want to contribute to the health and wellbeing of the patient. Remember someone, somewhere at 1:50 a.m. needs the product that you manufactured, your colleague tested, another QA-reviewed the batch record, materials management shipped with a label that I approved, and we all, with many others, ensured it met its safety, quality, identity, potency, and strength.

It's a reality when a patient says, "Without my medications I would not be able to carry out my typical day-to-day routines; I would have to rely on more assistance from others." — Maria Elsey, Registered General Nurse.

Graham P. Bunn

Editor

Graham P. Bunn is the president of GB Consulting LLC, in Pennsylvania, a company providing regulatory compliance, quality systems, regulatory action remediation, training and technical consulting services for pharmaceutical, biotechnology and other FDA and European Medicines Agency (EMA)-related industries. Before founding GB Consulting LLC, Graham gained broad good manufacturing practices (GMP) and FDA inspection experience through his work in the pharmaceutical industry, including working for SmithKline Beecham PLC (GlaxoSmithKline PLC), Wyeth Pharmaceuticals (Pfizer), and Astra Merck Inc. (AstraZeneca PLC). His career experience includes management positions and responsibilities as a corporate quality auditor and in quality assurance, validation, and clinical trials manufacturing and packaging. He has developed and facilitated numerous highly interactive learning and training workshops worldwide. Graham is also the author of several book chapters and journal articles. A member of the Regulatory Affairs Professional Society (RAPS). Graham received a BSc in pharmacy from Brighton University, England, and an MSc in quality assurance and regulatory affairs from Temple University, in Philadelphia.

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1 Status and Applicability of U.S. Regulations *CGMP*

Graham P. Bunn

CONTENTS

The Food and Drug Administration (FDA) is responsible for ensuring the quality of drug products by carefully monitoring drug manufacturers' compliance with Current Good Manufacturing Practice (CGMP) regulations. The CGMP regulations for drugs contain minimum requirements for the methods, facilities, and controls used in manufacturing, processing, and packing of a drug product. The regulations make sure that a product is safe for use, and that it has the ingredients and strength it claims to have. FDA's portion of the *CFR* is in Title 21, which interprets the *Federal Food, Drug and Cosmetic Act* (FD&C Act) and related statutes, including the Public Health Service Act.

The regulations discussed are primarily in Title 21 of the Code of Federal Regulations, which consists of nine volumes. The parts in these volumes are arranged in the following order: Parts 1–99, 100–169, 170–199, 200–299 (containing the bulk of the current good manufacturing practices [CGMPs], 300–499 (containing the bulk of the investigational new drug [IND] application, new drug application [NDA], and abbreviated new drug application [ANDA] materials), 500–599, 600–799, 800–1299, and 1300–end. This last volume addresses matters subject to the Drug Enforcement Administration (DEA), the Department of Justice (DOJ), and the Office of National Drug Control Policy.

The CGMP regulations (21 CFR 210–226) are promulgated by the Commissioner of the FDA under Section 701 (a) of the FD&C Act (21 USC 371 [a]) in furtherance of the requirement of Section 501(a)(2)(B) of the FD&C Act (21 USC 351[a][2][B]), which specifies that a drug is deemed adulterated "if the methods used in, or the facilities or the controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice." The purpose of Section 501(a)(2)(B) is to assure that such drug meets the requirements of the act as to safety and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess. The FDA is, of course, committed to various programs and systems designed to assure the quality of all drug products by careful monitoring of drug manufacturer's compliance with CGMP regulations. In order to identify their regulatees, Section 510(b) and (c) of the FD&C Act requires the registration of all producers of drugs and devices. Congressional language that accompanied this amendment stated it was "necessary to provide for the registration and inspection of all establishments in which drugs were manufactured, prepared, propagated, compounded, or processed" since these products were likely to enter interstate commerce. Section 510(h) requires that each registrant be inspected for compliance every two years.

FD&C Act Section Number	Title
Sec. 501	Sec. 351—Adulterated drugs and devices
Sec. 502	Sec. 352—Misbranded drugs and devices
Sec. 503	Sec. 353—Exemptions and consideration for certain drugs, devices, and biological products
Sec. 503A	Sec. 353a—Pharmacy compounding
Sec. 503A-1	Sec. 353a-1—Enhanced Communication
Sec. 503B	Sec. 353b—Outsourcing facilities
Sec. 505	Sec. 355—New drugs
	Sec. 355-1—Risk evaluation and mitigation strategies
Sec. 505D	Sec. 355e—Pharmaceutical security
Sec. 506A	Sec. 356a—Manufacturing changes
Sec. 510	Sec. 360—Registration of producers of drugs or devices
Sec. 511	Sec. 360a—Clinical trial guidance for antibiotic drugs
	Sec. 360a-1—Clinical trials

In recent years, the FDA has assumed additional roles for assurance to vendees through programs like the Government-Wide Quality Assurance Programs for drug purchase contracts by the Department of Defense and Veterans Affairs and the MAC program (Maximum Allowable Cost), a program that became seminal to the manufacture of generics. Their policy is outlined in the ORA (Office of Regulatory Affairs) Compliance Document Sec. 400.200 Consistent Application of CGMP Determinations (CPG 7132.12).[1]

Decisions regarding compliance with CGMP regulations are based on inspection of the facilities, sample analysis, and compliance history of the firm. These data are summarized in profiles that represent several years of history of the firms.

The CGMP deficiencies supporting regulatory action by the FDA also support decisions regarding nonapproval of NDA Supplements, as well as the purchasing contracts and candidacy for MAC; hence, some FDA expanded action is likely. Therefore, issuance of a "warning" letter or other regulatory action based on discovery of CGMP deficiencies must be accompanied by disapproval of any pending NDA, ANDA, or Supplement, or any government contract produced under the same deficiencies.

The FD&C Act applies to drugs introduced into interstate commerce in the United States, including drugs exported to or imported from other countries. Manufacturers in other countries who export to the United States are inspected either by the FDA or under reciprocal inspection agreements as part of the NDA approval process and antibiotic drug certification. Individual drug products are subjected to extensive examination, including laboratory testing, before being allowed into the United States.

On 1 November 2017, further aspects of the mutual recognition agreement between the European Union (EU) and the United States (US) was initiated to recognize inspections of manufacturing sites for human medicines conducted in their respective territories. This agreement, which updates the agreement from 1998, allows for recognition of each other's inspection outcomes and hence for better use of inspection expertise and resources. In June 2017, the European Commission confirmed that the US FDA had the capability, capacity, and procedures in place to carry out good manufacturing practice (GMP) inspections at a level equivalent to the EU. The FDA confirmed the capability of eight EU Member States (Austria, Croatia, France, Italy, Malta, Spain, Sweden, and United Kingdom). The remaining inspectorates will continue to be assessed until 15 July 2019.

The following was published on the FDA website in June 2018[2]:

> The Mutual Recognition Agreement (MRA) between FDA and European Union allows drug inspectors to rely upon information from drug inspections conducted within each other's borders. Under the Food and Drug Administration Safety and Innovation Act, enacted in 2012, FDA has the authority to enter into agreements to recognize drug inspections conducted by foreign regulatory authorities if the FDA determined those authorities are capable of conducting inspections that met US requirements. FDA and the EU have collaborated since May 2014 to evaluate the way they each inspect drug manufacturers and assess the risk and benefits of mutual recognition of drug inspections.
>
> **MRA**
>
> - Yields greater efficiencies for US and EU regulatory systems by avoiding duplication of inspections
> - Enables reallocation of resources towards inspection of drug manufacturing facilities with potentially higher public health risks across the globe
>
> FDA will continue to perform some inspections in EU countries with capable inspectorates, such as product manufacturing assessment inspections to support marketing approval decisions. However, FDA expects to perform fewer routine surveillance inspections in EU countries with a capable inspectorate.

The FDA has the authority to deny entry to any drug if there is a question regarding its safety, identity, strength, quality, or purity. This authority is exercised unless factory inspection is permitted or inspection information is available concerning nondomestic firms, in lieu of conducting foreign inspections. Although this authority is exercised more rarely and tempered by Chapter 8 of the Act, the FDA also has the authority to deny exit to questionable drugs.

Since the inception of the GMPs, the FDA strived to ensure that the regulated industries comply with a total control of product quality concept through its factory inspection programs and through participation in voluntary CGMP compliance seminars and workshops sponsored jointly with the industries or with educational institutions. As part of the FDA's Pharmaceutical CGMPs for the 21st Century Initiative, they have introduced quality systems and risk management approaches into existing programs. Regardless of the approaches used, the FDA wants the industry to prevent a drug product from being deemed adulterated under Section 501(a)(2)(B) and violative of Section 301(b) of the Food, Drug, and Cosmetic Act as is indicated by 21 CFR 211, Current Good Manufacturing Practice for Finished Pharmaceuticals.

§ 210.1 STATUS OF CURRENT GOOD MANUFACTURING PRACTICE REGULATIONS

a. *The regulations set forth in this part and in parts 211, 225, and 226 of this chapter contain the minimum current good manufacturing practice for methods to be used in, and the facilities or controls to be used for, the manufacture, processing, packing, or holding of a drug to assure that such drug meets the requirements of the act as to safety, and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess.*

b. *The failure to comply with any regulation set forth in this part and in parts 211, 225, and 226 of this chapter in the manufacture, processing, packing, or holding of a drug shall render such drug to be adulterated under section 501(a)(2)(B) of the act and such drug, as well as the person who is responsible for the failure to comply, shall be subject to regulatory action.*

c. *Owners and operators of establishments engaged in the recovery, donor screening, testing (including donor testing), processing, storage, labeling, packaging, or distribution of human cells, tissues, and cellular and tissue-based products (HCT/Ps), as defined in §1271.3(d) of this chapter, that are drugs (subject to review under an application submitted under section 505 of the act or under a biological product license application under section 351 of the Public Health Service Act), are subject to the donor-eligibility and applicable current good tissue practice procedures set forth in part 1271 subparts C and D of this chapter, in addition to the regulations in this part and in parts 211, 225, and 226 of this chapter. Failure to comply with any applicable regulation set forth in this part, in parts 211, 225, and 226 of this chapter, in part 1271 subpart C of this chapter, or in part 1271 subpart D of this chapter with respect to the manufacture, processing, packing, or holding of a drug, renders an HCT/P adulterated under section 501(a)(2)(B) of the act. Such HCT/P, as well as the person who is responsible for the failure to comply, is subject to regulatory action.*

[43 FR 45076, Sept. 29, 1978, as amended at 69 FR 29828, May 25, 2004; 74 FR 65431, Dec. 10, 2009]

§ 210.2 APPLICABILITY OF CURRENT GOOD MANUFACTURING PRACTICE REGULATIONS

a. *The regulations in this part and in parts 211, 225, and 226 of this chapter as they may pertain to a drug; in parts 600 through 680 of this chapter as they may pertain to a biological product for human use; and in part 1271 of this chapter as they are applicable to a human cell, tissue, or cellular or tissue-based product (HCT/P) that is a drug (subject to review under an application submitted under section 505 of the act or under a biological product license application under section 351 of the Public Health Service Act) shall be considered to supplement, not supersede, each other, unless the regulations explicitly provide otherwise. In the event of a conflict between applicable regulations in this part and in other parts of this chapter, the regulation specifically applicable to the drug product in question shall supersede the more general.*

b. *If a person engages in only some operations subject to the regulations in this part, in parts 211, 225, and 226 of this chapter, in parts 600 through 680 of this chapter, and in part 1271 of this chapter, and not in others, that person need only comply with those regulations applicable to the operations in which he or she is engaged.*

c. *An investigational drug for use in a phase 1 study, as described in 312.21(a) of this chapter, is subject to the statutory requirements set forth in 21 USC 351(a)(2)(B). The production of such drug is exempt from compliance with the regulations in part 211 of this chapter. However, this exemption does not apply to an investigational drug for use in a phase 1 study once the investigational drug has been made available for use by or for the sponsor in a phase 2 or phase 3 study, as described in 312.21(b) and (c) of this chapter, or the drug has been lawfully marketed. If the investigational drug has been made available in a phase 2 or phase 3 study or the drug has been lawfully marketed, the drug for use in the phase 1 study must comply with part 211.*

[69 FR 29828, May 25, 2004, as amended at 73 FR 40462, July 15, 2008; 74 FR 65431, Dec. 10, 2009]

§ 210.3 DEFINITIONS

a. *The definitions and interpretations contained in section 201 of the act shall be applicable to such terms when used in this part and in parts 211 through 226 of this chapter.*
b. *The following definitions of terms apply to this part and to parts 211 through 226 of this chapter.*
   1. *Act means the Federal Food, Drug, and Cosmetic Act, as amended (21 USC 301 et seq.).*
   2. *Batch means a specific quantity of a drug or other material that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture.*
   3. *Component means any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product.*
   4. *Drug product means a finished dosage form, for example, tablet, capsule, solution, etc., that contains an active drug ingredient generally, but not necessarily, in association with inactive ingredients. The term also includes a finished dosage form that does not contain an active ingredient but is intended to be used as a placebo.*
   5. *Fiber means any particulate contaminant with a length at least three times greater than its width.*
   6. *Nonfiber releasing filter means any filter, which after appropriate pretreatment such as washing or flushing, will not release fibers into the component or drug product that is being filtered.*
   7. *Active ingredient means any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect.*
   8. *Inactive ingredient means any component other than an active ingredient.*
   9. *In-process material means any material fabricated, compounded, blended, or derived by chemical reaction that is produced for, and used in, the preparation of the drug product.*
   10. *Lot means a batch, or a specific identified portion of a batch, having uniform character and quality within specified limits, or, in the case of a drug product produced by continuous process, it is a specific identified amount produced in a unit of time or quantity in a manner that assures its having uniform character and quality within specified limits.*

11. *Lot number, control number, or batch number means any distinctive combination of letters, numbers, or symbols, or any combination of them, from which the complete history of the manufacture, processing, packing, holding, and distribution of a batch or lot of drug product or other material can be determined.*
12. *Manufacture, processing, packing, or holding of a drug product includes packaging and labeling operations, testing, and quality control of drug products.*
13. *The term medicated feed means any Type B or Type C medicated feed as defined in § 558.3 of this chapter. The feed contains one or more drugs as defined in section 201(g) of the act. The manufacture of medicated feeds is subject to the requirements of part 225 of this chapter.*
14. *The term medicated premix means a Type A medicated article as defined in § 558.3 of this chapter. The article contains one or more drugs as defined in section 201(g) of the act. The manufacture of medicated premixes is subject to the requirements of part 226 of this chapter.*
15. *Quality control unit means any person or organizational element designated by the firm to be responsible for the duties relating to quality control.*
16. *Strength means:*
    i. *The concentration of the drug substance (for example, weight/weight, weight/volume, or unit dose/volume basis), and/or*
    ii. *The potency, that is, the therapeutic activity of the drug product as indicated by appropriate laboratory tests or by adequately developed and controlled clinical data (expressed, for example, in terms of units by reference to a standard).*
17. *Theoretical yield means the quantity that would be produced at any appropriate phase of manufacture, processing, or packing of a particular drug product, based upon the quantity of components to be used, in the absence of any loss or error in actual production.*
18. *Actual yield means the quantity that is actually produced at any appropriate phase of manufacture, processing, or packing of a particular drug product.*
19. *Percentage of theoretical yield means the ratio of the actual yield (at any appropriate phase of manufacture, processing, or packing of a particular drug product) to the theoretical yield (at the same phase), stated as a percentage.*
20. *Acceptance criteria means the product specifications and acceptance/rejection criteria, such as acceptable quality level and unacceptable quality level, with an associated sampling plan, that are necessary for making a decision to accept or reject a lot or batch (or any other convenient subgroups of manufactured units).*
21. *Representative sample means a sample that consists of a number of units that are drawn based on rational criteria, such as random sampling, and intended to assure that the sample accurately portrays the material being sampled.*
22. *Gang-printed labeling means labeling derived from a sheet of material on which more than one item of labeling is printed.*

[43 FR 45076, Sept. 29, 1978, as amended at 51 FR 7389, Mar. 3, 1986; 58 FR 41353, Aug. 3, 1993; 73 FR 51931, Sept. 8, 2008]

As described on the FDA Web page[1] at the time of writing:

> FDA ensures the quality of drug products by carefully monitoring drug manufacturers' compliance with its Current Good Manufacturing Practice (CGMP) regulations. The CGMP regulations for drugs contain minimum requirements for the methods, facilities, and controls used in manufacturing, processing, and packing of a drug product. The regulations make sure that a product is safe for use, and that it has the ingredients and strength it claims to have.

> The approval process for new and generic drug marketing applications includes a review of the manufacturer's compliance with the CGMPs. FDA assessors and inspectors determine whether the firm has the necessary facilities, equipment, and ability to manufacture the drug it intends to market.
>
> Code of Federal Regulations (CFR). FDA's portion of the CFR is in Title 21, which interprets the Federal Food, Drug and Cosmetic Act and related statutes, including the Public Health Service Act. The pharmaceutical or drug quality-related regulations appear in several parts of Title 21, including sections in parts 1–99, 200–299, 300–499, 600–799, and 800–1299.
>
> The regulations enable a common understanding of the regulatory process by describing the requirements to be followed by drug manufacturers, applicants, and FDA.

- 21 CFR Part 314 and Part 600. Application and licensing submission requirements for new and generic drug applicants.
- 21 CFR Part 210. Current Good Manufacturing Practice in Manufacturing Processing, packing, or Holding of Drugs.
- 21 CFR Part 211. Current Good Manufacturing Practice for Finished Pharmaceuticals.

The first paragraph, and repeated many other times on the FDA website, includes the identifiable phrase "…contain the minimum requirements for…" which are known to some recipients of warning letters, for example: "Your firm's planned corrections do not meet the minimum requirements of 21 CFR Parts 210 and 211, and there is no assurance that the drug products produced by your firm conform to the basic quality standards that ensure safety, identity, strength, quality, and purity."

FDA provides a brief introduction to the GMPs on the website[3] through a series of questions and answers:

> Pharmaceutical Quality affects every American. The Food and Drug Administration (FDA) regulates the quality of pharmaceuticals very carefully. The main regulatory standard for ensuring pharmaceutical quality is the Current Good Manufacturing Practice (CGMPs) regulation for human pharmaceuticals. Consumers expect that each batch of medicines they take will meet quality standards so that they will be safe and effective. Most people, however, are not aware of CGMPs, or how FDA assures that drug manufacturing processes meet these basic objectives. Recently, FDA has announced a number of regulatory actions taken against drug manufacturers based on the lack of CGMPs. This paper discusses some facts that may be helpful in understanding how CGMPs establish the foundation for drug product quality.

WHAT ARE CGMPs?

CGMP refers to the Current Good Manufacturing Practice regulations enforced by the FDA. CGMPs provide for systems that assure proper design, monitoring, and control of manufacturing processes and facilities. Adherence to the CGMP regulations assures the identity, strength, quality, and purity of drug products by requiring that manufacturers of medications adequately control manufacturing operations. This includes establishing strong quality management systems, obtaining appropriate quality raw materials, establishing robust operating procedures, detecting and investigating product quality deviations, and maintaining reliable testing laboratories. This formal system of controls at a pharmaceutical company, if adequately put into practice, helps to prevent instances of contamination, mix-ups, deviations, failures, and errors. This assures that drug products meet their quality standards.

The CGMP requirements were established to be flexible in order to allow each manufacturer to decide individually how to best implement the necessary controls by using scientifically sound design, processing methods, and testing procedures. The flexibility in these regulations allows companies to use modern technologies and innovative approaches to achieve higher quality through continual improvement. Accordingly, the "C" in CGMP stands for "current," requiring companies

to use technologies and systems that are up-to-date in order to comply with the regulations. Systems and equipment that may have been "top-of-the-line" to prevent contamination, mix-ups, and errors 10 or 20 years ago may be less than adequate by today's standards.

It is important to note that CGMPs are minimum requirements. Many pharmaceutical manufacturers are already implementing comprehensive, modern quality systems and risk management approaches that exceed these minimum standards.

WHY ARE CGMPs SO IMPORTANT?

A consumer usually cannot detect (through smell, touch, or sight) that a drug product is safe or if it will work. While CGMPs require testing, testing alone is not adequate to ensure quality. In most instances testing is done on a small sample of a batch (for example, a drug manufacturer may test 100 tablets from a batch that contains 2 million tablets), so that most of the batch can be used for patients rather than destroyed by testing. Therefore, it is important that drugs are manufactured under conditions and practices required by the CGMP regulations to assure that quality is built into the design and manufacturing process at every step. Facilities that are in good condition, equipment that is properly maintained and calibrated, employees who are qualified and fully trained, and processes that are reliable and reproducible, are a few examples of how CGMP requirements help to assure the safety and efficacy of drug products.

HOW DOES FDA DETERMINE IF A COMPANY IS COMPLYING WITH CGMP REGULATIONS?

FDA inspects pharmaceutical manufacturing facilities worldwide, including facilities that manufacture active ingredients and the finished product. Inspections follow a standard approach and are conducted by highly trained FDA staff. FDA also relies upon reports of potentially defective drug products from the public and the industry. FDA will often use these reports to identify sites for which an inspection or investigation is needed. Most companies that are inspected are found to be fully compliant with the CGMP regulations.

IF A MANUFACTURER IS NOT FOLLOWING CGMPs, ARE DRUG PRODUCTS SAFE FOR USE?

If a company is not complying with CGMP regulations, any drug it makes is considered "adulterated" under the law. This kind of adulteration means that the drug was not manufactured under conditions that comply with CGMP. It does not mean that there is necessarily something wrong with the drug.

For consumers currently taking medicines from a company that was not following CGMPs, FDA usually advises these consumers not to interrupt their drug therapy, which could have serious implications for their health. Consumers should seek advice from their health care professionals before stopping or changing medications. Regulatory actions against companies with poor CGMPs are often intended to prevent the possibility of unsafe and/or ineffective drugs. In rare cases, FDA regulatory action is intended to stop the distribution or manufacturing of violative product. The impact of CGMP violations depends on the nature of those violations and on the specific drugs involved. A drug manufactured in violation of CGMP may still meet its labeled specifications, and the risk that the drug is unsafe or ineffective could be minimal. Thus, FDA's advice will be specific to the circumstances, and health care professionals are best able to balance risks and benefits and make the right decision for their patients.

WHAT CAN FDA DO TO PROTECT THE PUBLIC WHEN THERE ARE CGMP VIOLATIONS?

If the failure to meet CGMPs results in the distribution of a drug that does not offer the benefit as labeled because, for example, it has too little active ingredient, the company may subsequently recall that product. This protects the public from further harm by removing these drugs from the market. While FDA cannot force a company to recall a drug, companies usually will recall voluntarily or at FDA's request. If a company refuses to recall a drug, FDA can warn the public and can seize the drug.

FDA can also bring a seizure or injunction case in court to address CGMP violations even where there is no direct evidence of a defect affecting the drug's performance. When FDA brings a seizure case, the agency asks the court for an order that allows federal officials to take possession of "adulterated" drugs. When FDA brings an injunction case, FDA asks the court to order a company to stop violating CGMPs. Both seizure and injunction cases often lead to court orders that require companies to take many steps to correct CGMP violations, which may include repairing facilities and equipment, improving sanitation and cleanliness, performing additional testing to verify quality, and improving employee training. FDA can also bring criminal cases because of CGMP violations, seeking fines and jail time.

HOW WOULD A NEW DRUG COMPANY LEARN ABOUT CGMPs AND ABOUT FDA'S EXPECTATIONS ON COMPLYING WITH THEM?

FDA publishes regulations and guidance documents for industry in the *Federal Register.* This is how the federal government notifies the public of what we are doing and why. FDA's website, www.fda.gov also contains links to the CGMP regulations, guidance documents, and various resources to help drug companies comply with the law. FDA also conducts extensive public outreach through presentations at national and international meetings and conferences, to discuss and explain the CGMP requirements and the latest policy documents.

The CGMP requirements were intentionally written with some vague terminology because as FDA points out they needed to be "…flexible in order to allow each manufacturer to decide individually how to best implement the necessary controls by using scientifically sound design, processing methods, and testing procedures." Companies are expected to use advances in technologies as they become available to enhance approaches to quality through continual improvement. The "C" in CGMP stands for "current," which requires companies to use technologies and systems to comply with the regulations that are current industry standards today but might be replaced or superseded in the future.

As described in the *Federal Register*[4], this general introduction to what is projected as a series of GMP regulations for all human drug products, as well as specific products or specific processes, is "intended to be general enough to be suitable for essentially all drug products, flexible enough to allow the use of sound judgment and permit innovation, and explicit enough to provide a clear understanding of what is required."

This approach places a large burden on pharmaceutical manufacturers, as adherence to the explicit regulations is a required minimum, but just by its use it is not adequate to ensure that a manufacturer is in compliance with the requirements. Additionally, manufacturers must be using current methods with current controls, thus setting as a requirement that which is overall current or generally accepted in the drug industry in relation to equipment, methodology, controls, and records. Thinking or allowing yourself as a manufacturer to be "average" in aspects and requirements, compared with the other manufacturers, still does not ensure compliance because the standard is not only that practices be "current" but that they also be "good." The introduction of a new practice, equipment, or acceptable standard/methodology that is "good" and enhances controls resets the industry standards.

Therefore, being in compliance with GMP is not a static situation but requires manufacturers to be aware not only of what is current in the industry but also to be aware of innovations that may be "good." FDA is conscious of these continuous changes within the industry and may reflect them in the "current" GMP interpretations.

Pharmaceutical manufacturers are expected to have processes in place to remain current with the changing regulatory environment in the countries/markets that their products are marketed by evaluating the changes and determining if, what, and when they need to make changes. Some changes may not require any actions because they may already be accommodated or not apply.

THE MEANING OF "CURRENT"

The most unique and interesting part of the GMP regulations is determining exactly what is "current" for GMPs.

Congress intended that the phrase itself (current good manufacturing practice) have a unique meaning. The FDA determines what constitutes "current good manufacturing practice" based upon its experience with the manufacture of drugs through inspectional and compliance activities. Although the practices must be "current" in the industry, they need not be widely prevalent. FDA notes[5]

> CGMP refers to the Current Good Manufacturing Practice regulations enforced by the FDA. CGMPs provide for systems that assure proper design, monitoring, and control of manufacturing processes and facilities. Adherence to the CGMP regulations assures the identity, strength, quality, and purity of drug products by requiring that manufacturers of medications adequately control manufacturing operations. This includes establishing strong quality management systems, obtaining appropriate quality raw materials, establishing robust operating procedures, detecting and investigating product quality deviations, and maintaining reliable testing laboratories. This formal system of controls at a pharmaceutical company, if adequately put into practice, helps to prevent instances of contamination, mix-ups, deviations, failures, and errors. This assures that drug products meet their quality standards.
>
> The CGMP requirements were established to be flexible in order to allow each manufacturer to decide individually how to best implement the necessary controls by using scientifically sound design, processing methods, and testing procedures. The flexibility in these regulations allows companies to use modern technologies and innovative approaches to achieve higher quality through continual improvement. Accordingly, the "C" in CGMP stands for "current," requiring companies to use technologies and systems that are up-to-date in order to comply with the regulations. Systems and equipment that may have been "top-of-the-line" to prevent contamination, mix-ups, and errors 10 or 20 years ago may be less than adequate by today's standards.
>
> It is important to note that CGMPs are minimum requirements. Many pharmaceutical manufacturers are already implementing comprehensive, modern quality systems and risk management approaches that exceed these minimum standards.

The FDA also notes that, although it does not manufacture drugs, it has the unique ability to determine CGMPs for drugs, since it alone has access to the facilities and records of every manufacturer of pharmaceuticals in the United States and the drug regulatory filings for all products sold in the United States. Given the fact that many processes and controls are considered by manufacturers to be trade secrets, their competitors are not likely to discover what nonpublic practices are current.

Even if current practices were available, the FDA holds that it has special technical and scientific expertise to determine which of the current practices are also "good." This expertise is inherent in reviews of production and control techniques in NDAs and ANDAs, supplemental applications, antibiotic certification forms, biological establishment and product licenses, new

animal drug applications, and proposed and final compendial standards. Additional experience is based on establishment inspection reports filed by FDA investigators and the monitoring of drug recalls.

A current, although not necessarily predominant, practice is considered "good" if:

1. It is feasible for manufacturers to implement.
2. It contributes to ensuring the safety, quality, or purity of the drug product.
3. The value of the contributions or added assurance exceeds the cost in money or other burdens of implementing or continuing the practice.

It is worthwhile remembering, as all of us working in the industry are also consumers sometime during our life.

FDA publishes regulations and guidance documents for industry in the *Federal Register*. This is how the federal government notifies the public of what they are doing and why.

ROLE AND IMPORTANCE OF THE UNITED STATES PHARMOCOPEIA

The *United States Pharmacopeia* (USP) is a pharmacopeia published annually by the United States Pharmacopeial Convention and is published in a combined volume with the *National Formulary* as the USP–NF. A drug ingredient or drug product having an applicable USP quality standard monograph must conform in order to use the designation "USP" or "NF." The USP–NF standards also have a role in US federal law; a drug or drug ingredient recognized in USP–NF is considered adulterated if it does not satisfy compendial standards for strength, quality, or purity.

The role of the USP is of course not limited to the United States. This was true even prior to the time it became incorporated within the FD&C Act for its ultimate importance in dealing with such portions of that law that recite prohibited acts.

About the USP: The US Pharmacopeial Convention is an independent, nonprofit organization that safeguards the public's health by developing quality standards for medicines, dietary supplements, and food ingredients.

USP–FDA Shared History and Mission: The USP–FDA relationship dates back to the 1906 Pure Food and Drug Act, which deemed the *United States Pharmacopeia* and the *National Formulary* official compendia under federal law.

How USP and FDA Work Together: USP and FDA maintain official contact through a number of established channels:

- Five FDA centers and the Office of the Commissioner have established delegates at USP's Convention, the top leadership body of our organization.
- USP staff maintain executive-level contacts with FDA leadership and routine contacts with FDA's Compendial Operations and Standards Branch through quarterly meetings.
- More than 100 FDA staff participate as government liaisons on USP's Expert Committees and Expert Panels, the scientific bodies that develop and revise USP's written and physical standards.

Government liaisons represent FDA opinions and viewpoints (as opposed to other USP volunteers, who represent their own opinions rather than their employers') at public USP meetings such as the Expert Committee Meetings, Expert Panels, and Stakeholder Forums.

The Importance of USP–FDA Collaboration: FDA-USP collaboration is essential to ensure appropriate quality standards and, where applicable, standards that reflect FDA-approved product quality standards.

The FDA Office of Regulatory Affairs/USP Cooperative Research and Development Agreements enable USP and FDA to collaborate on protocols and work plans that impact the effective development of up-to-date monographs and nomenclature.

FDA and USP work together to identify areas for monograph or general chapter development where there is a need for quality issues to be addressed. Our interactions lead to a more efficient standards development process.

USP's Role Under the Federal Food, Drug, and Cosmetic Act: USP standards are an integral part of the patient safety framework:

- The Federal Food, Drug, and Cosmetic Act (Act) expressly recognizes USP quality standards for medicines.
- Under the "Act," USP standards are binding for dietary supplement manufacturers that label their products as compliant with USP specifications.
- FDA has issued more than 200 regulations for food substances that incorporate USP's *Food Chemicals Codex* specifications by reference.

Compendial standards remain connected to FDA provisions in the Act and other consumer protection laws, regulations and guidance that have been part of the important safeguards that make medicines, dietary supplements and food ingredients in the U.S. among the safest in the world.[6]

Key milestones in USP history:[7] Established in 1820 "to ensure that consumers receive medicines of the highest possible quality, strength, and purity in the United States," it was destined to reflect medical and pharmaceutical advances from the major European laboratories and academia from the first. In 1900, USP incorporates and sets up a Board of Trustees. This establishes USP as a sustainable, nonprofit organization with the goal of protecting public health. Then in 1906 the Food and Drugs Act mandates that drugs meet the standards of strength, quality, and purity stipulated in the USP and NF. The year 1941 saw the USP develop an insulin Reference Standard, which ensures continued production and access. By 1969, the USP is recognized in 27 countries and serves as the sole standard in Costa Rica, El Salvador, and Panama. In 1994, the Dietary Supplements Health and Education Act (DSHEA) names USP and NF as official compendia for dietary supplements. Products that suppliers represent as confirming to USP standards may be deemed misbranded if they fail to conform. In 2001, USP launches its Dietary Supplement Verification Program, followed by the Dietary Ingredient Verification Program (2004), and the Pharmaceutical Ingredient Verification Program (2006). These assure customers that the dietary and pharmaceutical ingredients are of the highest quality. A significant event in 2007 resulted in the USP working with regulators and industry to control potential impurities by revising monograph methods and introducing new Reference Standards to help thwart adulteration of the global heparin supply. The year 2013 sees the USP create the Herbal Medicines Compendium, a freely available, online resource that provides standards for herbal ingredients used in herbal medicines. Then in 2017, USP and USAID celebrate 25 years of collaborating to help developing countries address critical issues related to medicines information and quality.

Located nearby the FDA in Rockville, Maryland, USA, they can be reached at 301-998-6821 or at: http://www.usp.org.

USP develops and publishes standards for drug substances, drug products, excipients, and dietary supplements in the United States Pharmacopeia–National Formulary (USP–NF). These standards have been recognized in the Federal Food, Drug and Cosmetic (FD&C) Act since it was first enacted in 1938. The FD&C Act defines the term "official compendium" as the official USP, the official NF, the official Homeopathic Pharmacopeia of the United States, or any Supplement to them. USP–NF standards play a role in the adulteration and misbranding provisions of the FD&C Act (which apply as well to biologics, a subset of drugs, under the Public Health Service Act). USP has no role in enforcement of these or other provisions that recognize USP–NF standards, which is the responsibility of FDA and other government authorities in the United States and elsewhere. Manufacturers and potentially affected parties are encouraged to contact FDA with questions about the specific applicability of USP standards to their products.

All proposed revisions to USP–NF standards are published for review and comment in a USP publication, *Pharmacopeia Forum*.

SPECIFIC DRUG CATEGORIES AND TOPICS

- **Drugs:** USP's goal is to have substance and preparation (product) monographs in USP–NF for all FDA-approved drugs, including biologics and their ingredients. USP also develops monographs for therapeutic products not approved by FDA, for example, pre-1938 drugs, dietary supplements, and compounded preparations. Although submission of information needed to develop a monograph by the Council of Experts is voluntary, compliance with a USP–NF monograph, if available, is mandatory in the following respects:
- **Nonproprietary Name:** Under the relevant FD&C Act provisions, a drug will be deemed misbranded unless its label bears to the exclusion of any other nonproprietary name the "established" name, which ordinarily is the compendial name (see discussion of nomenclature below).
- **Identity:** A drug with a name recognized in USP–NF must comply with the identity/identification requirements of its monograph, or be deemed adulterated, misbranded, or both.
- **Strength, Quality, Purity:** Drugs also must comply with compendial standards for strength, quality, and purity (tests for assay and impurities), unless labeled to show all respects in which the drugs differ. FDA requires that names for articles that are not official must be clearly distinguishing and differentiating from any name recognized in an official compendium.
- **Packaging, Labeling:** Drugs with a name recognized in USP–NF also will be considered misbranded unless they meet compendial standards for packaging and labeling.

The USP Reference Standards are highly characterized specimens of drug substances, major impurities, degradation products, and performance calibrators for use in testing drugs and nutritional supplements. They are used to perform official methods of analysis in pharmaceutical testing. The manufacturer may use other than the official method of analysis, but the substance used and the product manufactured must meet the official specifications contained in the USP–NF, following the official method of analysis. USP Material Safety Data Sheets are available to purchasers of standards. The USP also tests and distributes other authenticated substances not currently included in the USP–NF that are still in sufficient demand; FCC Reference Standards specified in the latest edition of the Food Chemicals Codex; and highly purified samples of chemicals, including drugs of abuse. The USP website http://www.usp.org has links to Reference Standards, USP–NF, Patient Safety, and USP-Verified and other topics.

Continuous update acquisition of official and unofficial compendia is necessary to remain current with CGMPs, and the law requires that products meet the requirements of the USP–NF for the monographs applicable to their products as labeled. It is typical for many revisions to occur in USP–NF Supplements and Editions. However, it is the responsibility of the drug manufacturer to keep ahead of the proposed changes, assess potential impacts, and take appropriate actions.

On the FDA website[8] there is a response to the question relating to the relationship between the USP and FDA guidance:

Are USP general chapters above <999> considered equivalent to FDA guidance? What is their purpose and how should manufacturers use these informational chapters?

"No, FDA is the only source of policy on pharmaceutical CGMPs and quality. CGMP requirements are found in statutes and regulations, and FDA's current thinking on these requirements is explained in the Agency's guidance documents.

The US Pharmacopeial Convention is a private, nongovernmental organization that publishes the United States Pharmacopeia (USP) and the National Formulary (NF) as official compendia of the United States. Although much of the USP and NF is legally enforceable, the USP general chapters numbered above <999> (general information chapters) are informational and generally do not contain any mandatory requirements (see USP General Notices 2.10). General information chapters might include some recommendations that may help a firm meet CGMPs."

RECENT FOOD AND DRUG ADMINISTRATION DRUG-RELATED MILESTONES

This section has been revised and includes those specifically for compounded drug products. A history of regulations can be found on the FDA website www.FDA.gov

2000

The US Supreme Court, upholding an earlier decision in *Food and Drug Administration v. Brown Williamson Tobacco Corp. et al.,* ruled 5–4 that FDA does not have authority to regulate tobacco as a drug. Within weeks of this ruling, FDA revoked its final rule, issued in 1996, that restricted the sale and distribution of cigarettes and smokeless tobacco products to children and adolescents, and that determined that cigarettes and smokeless tobacco products are combination products consisting of a drug (nicotine) and device components intended to deliver nicotine to the body.

Federal agencies are required to issue guidelines to maximize the quality, objectivity, utility, and integrity of the information they generate, and to provide a mechanism whereby those affected can secure correction of information that does not meet these guidelines, under the Data Quality Act.

Publication of a rule on dietary supplements defines the type of statement that can be labeled regarding the effect of supplements on the structure or function of the body.

2002

The Best Pharmaceuticals for Children Act improves safety and efficacy of patented and off-patent medicines for children. It continues the exclusivity provisions for pediatric drugs as mandated under the Food and Drug Administration Modernization Act of 1997, in which market exclusivity of a drug is extended by six months, and in exchange the manufacturer carries out studies of the effects of drugs when taken by children. The provisions both clarify aspects of the exclusivity period and amend procedures for generic drug approval in cases when pediatric guidelines are added to the labeling.

In the wake of the events of September 11, 2001, the Public Health Security and Bioterrorism Preparedness and Response Act of 2002 is designed to improve the country's ability to prevent and respond to public health emergencies, and provisions include a requirement that FDA issue regulations to enhance controls over imported and domestically produced commodities it regulates.

Under the Medical Device User Fee and Modernization Act, *fees are assessed to sponsors of* medical device applications for evaluation, provisions are established for device establishment inspections by accredited third-parties, and new requirements emerge for reprocessed single-use devices.

The Office of Combination Products is formed within the Office of the Commissioner, as mandated under the Medical Device User Fee and Modernization Act, to oversee review of products that fall into multiple jurisdictions within the FDA.

An effort to enhance and update the regulation of manufacturing processes and end-product quality of animal and human drugs and biological medicines is announced: the CGMP initiative. The goals of the initiative are to focus on the greatest risks to public health in manufacturing procedures, to ensure that process and product quality standards do not impede innovation, and to apply a consistent approach to these issues across the FDA.

2003

The Medicare Prescription Drug Improvement and Modernization Act requires, among other elements, that a study be made of how current and emerging technologies can be utilized to make essential information about prescription drugs available to the blind and visually impaired.

The Animal Drug User Fee Act permits the FDA to collect subsidies for the review of certain animal drug applications from sponsors, analogous to laws passed for the evaluation of other products the FDA regulates, ensuring the safety and effectiveness of drugs for animals and the safety of animals used as foodstuffs.

The FDA is given clear authority under the Pediatric Research Equity Act to require that sponsors conduct clinical research into pediatric applications for new drugs and biological products.

2004

Project BioShield Act of 2004 authorizes the FDA to expedite its review procedures to enable rapid distribution of treatments as countermeasures to chemical, biological, and nuclear agents that may be used in a terrorist attack against the United States, among other provisions.

A ban on over-the-counter steroid precursors, increased penalties for making, selling, or possessing illegal steroids precursors, and funds for preventive education to children are features of the Anabolic Steroid Control Act of 2004.

The FDA publishes "Innovation or Stagnation?—Challenge and Opportunity on the Critical Path to New Medical Products," which examines the critical path needed to bring therapeutic products to fruition, and how the FDA can collaborate in the process, from laboratory to production to end use, to make medical breakthroughs available to those in need as quickly as possible.

On the basis of recent results from controlled clinical studies indicating that Cox-2 selective agents may be connected to an elevated risk of serious cardiovascular events, including heart attack and stroke, the FDA issues a public health advisory urging health professionals to limit the use of these drugs.

To provide for the treatment of animal species other than cattle, horses, swine, chickens, turkeys, dogs, and cats, as well as other species that may be added at a later time, the Minor Use and Minor Species Animal Health Act is passed to encourage the development of treatments for species that would otherwise attract little interest in the development of veterinary therapies.

Deeming such products to present an unreasonable risk of harm, the FDA bans dietary supplements containing ephedrine alkaloids based on an increasing number of adverse events linked to these products and the known pharmacology of these alkaloids.

2005

Formation of the Drug Safety Board is announced, consisting of FDA staff and representatives from the National Institutes of Health and the Veterans Administration. The Board will advise the director, Center for Drug Evaluation and Research, and the FDA on drug safety issues and work with the agency in communicating safety information to health professionals and patients.

2006

FDA approves final rule, Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products.

New content and format requirements make it easier for health-care professionals to access, read, and use information in FDA-approved labeling.

2009

President Obama signs the Family Smoking Prevention and Tobacco Control Act into law. The Tobacco Control Act gives FDA authority to regulate the manufacture, distribution, and marketing of tobacco products to protect public health.

FDA Center for Tobacco Products established.
FDA announced a ban on cigarettes with flavors characterizing fruit, candy, or clove.

2012

Food and Drug Administration Safety and Innovation Act (FDASIA). Expands FDA authorities to collect user fees from industry to fund reviews of innovator drugs, medical devices, generic drugs, and biosimilar biological products; promotes innovation to speed patient access to safe and effective products; increases stakeholder involvement in FDA processes; and enhances the safety of the drug supply chain.

Medical Device User Fee and Modernization Act (MDUFMA III). As part of FDASIA, reauthorizes user fees from industry to fund reviews of medical devices in exchange for FDA to meet certain performance goals.

In 2012, an outbreak of fungal meningitis linked to a contaminated compounded drug product resulted in the loss of 64 lives and caused more than 751 illnesses. In response, Congress enacted the 2013 Drug Quality and Security Act (DQSA) that insures greater regulatory oversight of facilities creating compounded drugs. Among other provisions it outlines steps for an electronic and interoperable system to identify and trace certain prescription drugs throughout the United States.

2013

Pandemic and All-Hazards Preparedness Reauthorization Act (PAHPRA). Establishes and reauthorizes certain programs under the Public Health Service Act and the Food, Drug, and Cosmetic Act with respect to public health security and all-hazards preparedness and response.

OBTAINING FOOD AND DRUG ADMINISTRATION REGULATIONS

The FDA's regulations are printed in Title 21, Code of Federal Regulations (21 CFR). In addition, the FDA and other government agencies publish new regulations and proposals in the *Federal Register* throughout the year. Readers may purchase the books in 21 CFR from the US Government Printing Office.

THE *FEDERAL REGISTER*

The *Federal Register* is published Monday through Friday by the US Government Printing Office in paper and microfiche editions, and as a database on Internet.

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2. https://www.fda.gov/internationalprograms/agreements/ucm598735.htm.
3. https://www.fda.gov/drugs/developmentapprovalprocess/manufacturing/ucm169105.htm.
4. Federal Register, Vol. 43, No. 190 - Friday, September 29, 1978: Chapter I-Food and Drug Administration Department of Health, Education, and Welfare Subchapter C-Drugs: General [Docket No. 75n-0339] Human and Veterinary Drugs Current Good Manufacturing Practice in Manufacture, Processing, Packing, or Holding.
5. Facts About the Current Good Manufacturing Practices (cGMPs): Available at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm169105.htm.
6. www.USP.org.

7. http://www.usp.org/about/usp-timeline.
8. Questions and Answers on Current Good Manufacturing Practices–General Provisions. Available at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm124747.htm.

SUGGESTED READINGS

- FDA Guidance for Industry: Quality Systems Approach to Pharmaceutical CGMP Regulations, Rockville, MD, US Dept. of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, 2006, www.FDA.gov
- Core Guideline Draft: Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management, 2017, www.FDA.gov
- FDA Guidance for Industry: Advancement of Emerging Technology Applications for Pharmaceutical Innovation and Modernization, September 2017, www.FDA.gov
- FDA Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products, January 2017, www.FDA.gov
- FDA Draft Guidance for Industry: Request for Quality Metrics, June 2016, www.FDA.gov.
- 21 CFR Part 111 entitled 'Current Good Manufacturing Practice (CGMP) In Manufacturing, Packaging, Labeling, Or Holding Operations For Dietary Supplements' (72 FR 34752).
- FDA Draft Guidance for Industry: Current Good Manufacturing Practice—Interim Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act, July 2014, www.FDA.gov
- FDA Guidance for Industry: Contract Manufacturing Arrangements for Drugs: Quality Agreements, November 2016, www.FDA.gov

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