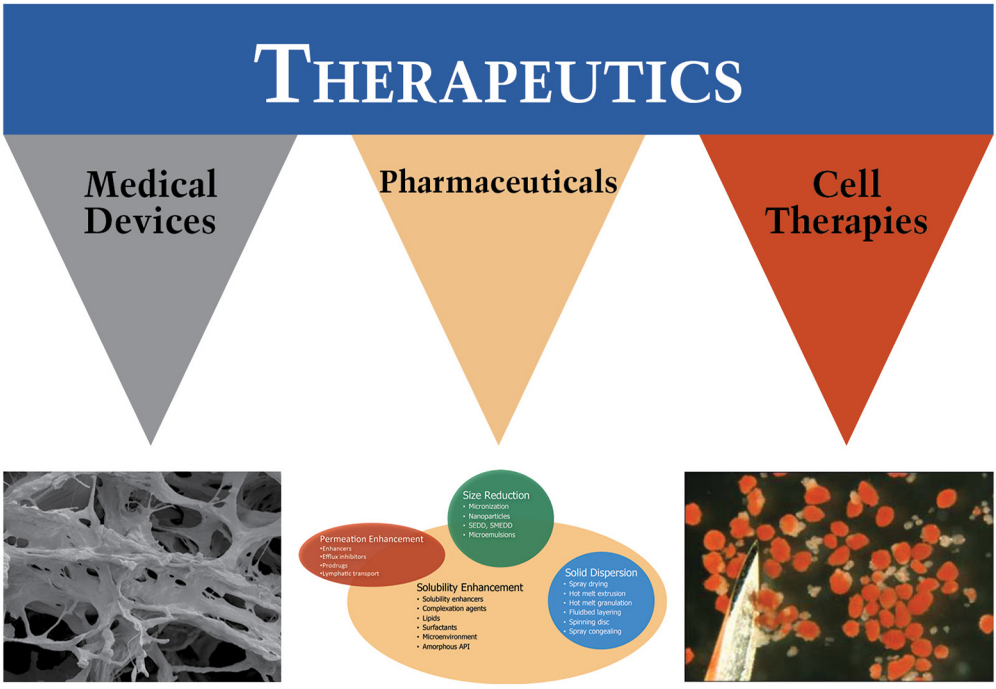
Therapeutic Delivery Solutions

Edited By **Chung Chow Chan, Kwok Chow, Bill McKay & Michelle Fung**



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THERAPEUTIC DELIVERY SOLUTIONS

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PREFACE

The technologies for the administration of therapeutic agents have been traditionally led by the pharmaceutical industry that develops drug molecules (both small and large molecules) in various dosage forms. The medical device industry has also evolved to apply its technologies to deliver drugs to various target sites.

Cellular therapy is now rapidly emerging as a new therapeutic solution platform, analogous to dosage form design and device development, in the last few decades. Under the Executive Order 13505 of March 9, 2009, in the United States, President Obama's Administration is committed to supporting and conducting ethically responsible, scientifically worthy human stem cell research, including human embryonic stem cell research. "National Institutes of Health Guidelines for Human Stem Cell Research" (Guidelines), effective July 7, 2009, applies to research using human embryonic stem cells and certain uses of human-induced pluripotent stem cells that have the potential to improve our understanding of human biology and aid in the discovery of new ways to prevent and treat illness. Researches in cellular therapy, for example, stem cells, have had very promising results as therapeutic solutions to diseased states and organ transplants.

This textbook provides a convergent link between traditional dosage form design, medical device development, and cellular therapeutics. It attempts to bring these three platforms of therapeutic delivery solution development together in one place to show the potential idiosyncrasies and common and dissimilar challenges that each platform faces to provide the best therapeutic delivery solution to the patient. Contemporary scientific and medical information as well as the newly emerging regulatory scientific information are discussed. This textbook will provide development scientists and medical professionals more options to develop a therapeutic agent to its fullest potential and create better and more creative therapeutic solutions.

The content of the book is grouped into five sections. Section 1 (consisting of Chapter 1) introduces the requirements and issues encountered in regulatory submissions in the pharmaceutical, cellular/gene products, and medical device industries. Section 2 (consisting of Chapters 2 and 3) explains in detail the traditional pharmaceutical drug therapy development. Section 3 (consisting of Chapters 4–6) provides an overview, current trends, and strategies of special medical device development. Section 4 (consisting of Chapters 7–9) introduces the reader to the latest advances and innovations in cellular and stem cell therapeutic delivery. Section 5 (consisting of Chapters 10–14) provides information on the analytical support needed for the research and development in Sections 2–4.

Chapter 1 provides an overview of the current regulatory requirements for the development of the three platforms of therapeutic solution and new FDA initiatives to ensure that innovative products reach the patients who need them and when they need them.

An overview of the approach and strategies for development of immediate release tablets after a drug candidate is selected is provided in Chapter 2. Chapter 3 discusses the strategies (with examples) for the development of low aqueous solubility drug products.

Chapter 4 starts with an overview, key trends, and drivers for drug delivery medical devices. Chapter 5 focuses on the local growth factor delivery to address metabolic bone disorders. "From glass syringes to feedback-controlled patch pumps", Chapter 6 discusses the amazing accomplishment for the pharmaceutical and medical device industries with the insulin pump to continuously deliver precise amounts of insulin 24 h a day.

Cell-based biologic therapies have a long history. Simple blood transfusions and tissue transplants are commonly utilized in medical practice. Chapter 7 reviews the history of islet transplantation, procedural issues, current outcomes, and future directions. Chapter 8 provides an overview of the latest developments of cell-based biologic therapies and discusses the future outlook for these novel treatment modalities, for example, cancer, infection, and autoimmune disorders. Chapter 9 reviews the history of stem cell research and development, sources of various stem cells (e.g., neonatal, adult, reprogrammed), technical and regulatory issues of stem cell therapy, and the prospect of industrialization of stem cell technology into future medical therapy.

Chapters 10 to 14 provide the analytical support needed in the development of the three platforms of therapeutic solution delivery. Chapter 10 summarizes the specifications setting and stability studies requirements for development work. Chapter 11 shows how LC–MS techniques have been used in all stages of the drug development process including discovery, preclinical, clinical, and manufacturing. Chapter 12 discusses the importance of biorelevant methods and how to achieve them. Chapter 13 provides information and importance of ICH guidelines for development and global harmonization. In the development of therapeutic solution, there will be situations when out of specification (OOS) or aberrant data are obtained. Chapter 14 looks at how the use of sound scientific judgment and good documentation can lead to a successful OOS/atypical result investigation in a case study according to current guidance.

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SECTION 1

REQUIREMENTS AND ISSUES ENCOUNTERED IN REGULATORY SUBMISSIONS IN THE PHARMACEUTICAL, CELL THERAPY AND MEDICAL DEVICE INDUSTRIES

1

CHALLENGES TO QUALITY AND REGULATORY REQUIREMENT IN THE UNITED STATES—DRUGS, MEDICAL DEVICE, AND CELL THERAPY

CHUNG CHOW CHAN, SULTAN GHANI, IAIN SIMPSON, AND JAMES BLAKEMORE

1.1 OVERVIEW OF REGULATORY REQUIREMENTS FOR PHARMACEUTICAL, MEDICAL DEVICE, AND CELL THERAPIES

The technologies for the administration of therapeutic agents had been traditionally led by the pharmaceutical industry, which develops small drug molecules into various dosage forms. These developments have been followed by large-molecule pharmaceutical development (proteins, etc.), device development, and the new emerging cellular therapy. Recent breakthroughs in science and technology (ranging from sequencing of the human genome to advances in the application of nanotechnology to new medical products) are transforming the ability to treat diseases and bring with it new challenges in regulatory approval.

This chapter brings together the regulatory requirements for the development of the three platforms of therapeutic delivery solution (pharmaceutical, medical devices, and cellular therapeutic solutions) to illustrate the common/different strategies of regulating these three therapeutic deliveries and the current initiatives initiated in the United States and other countries. Note that the terms "drugs" and "pharmaceuticals" will be used interchangeably in this chapter. The common goal for all three platforms

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of delivery is current Good Manufacturing Practices (CGMP). The detailed process of achieving the common goal of GMP is different in each therapeutic area. The summary of the common regulatory requirements and the different approaches to reach this goal are presented.

The evaluation and approval processes are being modernized by the Food and Drug Administration (FDA) in the United States and other global regulatory agencies to ensure that innovative products reach the patients who need them and when they need them. In the United States, this is being done through advancing Regulatory science, which is the science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of FDA-regulated products [1].

In the United States, drug delivery is regulated by the Code of Federal Regulations (CFR). CFR is the codification of the general and permanent rules and regulations. This is published in the Federal Register by the executive departments and agencies of the Federal Government. It is divided into 50 titles that represent broad areas subject to Federal regulation.

Each title is divided into chapters, which usually bear the name of the issuing agency. Each chapter is further subdivided into parts that cover specific regulatory areas. Large parts may be subdivided into subparts. All parts are organized in sections, and most citations in the CFR are provided at the section level (http://www.gpo.gov/).

Title 21 of the CFR is reserved for Food and Drug under the rules of the FDA, Department of Health and Administrative Services. Title 21 contains the following three chapters:

- Chapter I—Food and Drug Administration, Department of Health and Human Services (Parts 1–1299)
- Chapter II—Drug Enforcement Administration, Department of Justice (Parts 1300–1321)
- Chapter III—Office of National Drug Control Policy (Parts 1400–1499)

1.2 REGULATORY REQUIREMENTS AND CHALLENGES FOR PHARMACEUTICAL, MEDICAL DEVICE, AND CELL THERAPIES

Title 21 Chapter 1 contains Parts 1–1299. The parts that are commonly encountered in the development of the three platforms of therapeutic delivery are listed below:

Part 3—Product Jurisdiction

Part 4—Current Good Manufacturing Practice Requirements for Combination Products (effective July 2013)

Part 11—Electronic Records; Electronic Signatures

Part 26—Mutual Recognition of Pharmaceutical Good Manufacturing Practice Reports, Medical Device Quality System Audit Reports, and Certain Medical

Device Product Evaluation Reports: United States and the European Community

Part 58—Good Laboratory Practice for Nonclinical Laboratory Studies

Part 210—Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; General

Part 211—Current Good Manufacturing Practice for Finished Pharmaceuticals

Part 312—Investigational New Drug Application

Part 600—Biological Products: General

Part 601—Biologic License Application

Part 610—General Biological Products Standards

Part 820—Quality System Regulation (Devices)

Part 814—Premarket Approval of Medical Devices

Part 1270—Human Tissue Intended for Transplantation

Part 1271—Human Cells, Tissues, and Cellular and Tissue-Based Products

In the United States, the regulatory requirements of the three platforms of drug delivery are implemented through three separate Centers in the FDA:

1. Center for Drug Evaluation and Research (CDER) for Pharmaceuticals. CDER's primary mission is to make certain that safe and effective drugs are available to the American people.
2. Center for Devices and Radiological Health (CDRH) for Medical Devices. CDRH is responsible for ensuring the safety and effectiveness of medical devices and eliminating unnecessary human exposure to man-made radiation from medical, occupational, and consumer products. It will advance public health and facilitate innovation to help bring novel technologies to market and make the medical devices that are already on the market safer and more effective.
3. Center for Biologics Evaluation and Research (CBER) for Cell Therapy. CBER regulates biological products for human use and protects and advances the public health by ensuring that biological products are safe and effective and available to those who need them.

Whether the item is a pharmaceutical agent, cell delivery agent, or medical device, it shares the common criteria in the regulatory approval of intended use of the product and CGMP. Pharmaceutical and cell therapy products share many common processes and techniques to provide relief to disease states of the patient. Device products are more varied and range from simple household products to highly sophisticated imaging products, which may provide other use in addition to providing relief to disease states. However, it still needs to fulfill the common criteria of intended use and be safe to the patients. As an example, a simple device product (Shoulder/Flex Massager) was used to "help relieve muscle pain" (intended use). However, because of incidents related to its safety (report of strangulation and death) at the time of its intended use, the product had been voluntarily recalled by the manufacturer [2].

1.2.1 Center for Drug Evaluation and Research

CDER enforces CGMP through Part 211 by implementing the regulatory sections tabulated in Table 1.1. Section 501(a)(2)(B) of the Food and Drug Act (FD&C Act) requires drugs, which include investigational new drug (IND) products, to comply with CGMP as follows:

> A drug…shall be deemed adulterated…if…the methods used in, or the facilities or 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 to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess.

Based on the statutory requirement for manufacturers to follow CGMP, FDA issued CGMP regulations for drug and biological products [3]. Although FDA stated at the time of issuance that the regulations applied to all types of pharmaceutical production, the preamble to the regulations indicated that FDA was considering proposing additional regulations governing drugs used in investigational clinical trials.

Because certain requirements in Part 211, which implement Section 501(a)(2)(B) of the FD&C Act, were directed at the commercial manufacture of products typically characterized by large, repetitive, commercial batch production (e.g., those regulations that address validation of manufacturing processes) and warehousing, they may not be appropriate to the manufacture of most investigational drugs used for Phase 1 clinical trials. Guidances on GMP requirements are now available for Phase 1–3 studies.

1.2.2 Center for Devices and Radiological Health

Medical devices employ a diversity of technologies to give a wide array of products in the healthcare sector. They range from simple devices such as bandages to life-maintaining active implantable devices such as insulin pump or heart pacemakers to sophisticated diagnostic imaging and surgical equipment. CDRH enforces CGMP through Part 820 by enforcing the regulatory requirements tabulated in Table 1.2. The quality system regulation of 820 govern the methods used in, and the facilities and controls used for, the design, manufacture, packaging, labeling, storage, installation, and servicing of all finished devices intended for human use. The requirements in this part are intended to ensure that finished devices will be safe and effective and otherwise in compliance with the FD&C Act.

Certain issues have arisen often relating to whether a product should be classified as a drug or a device. In Europe, the manufacturer is responsible for the classification of medical devices. In the United States, FDA is responsible for the classification of the medical devices. Accordingly, in the United States, a draft guidance document has been issued to focus particularly on when a product may be classified as a drug or a device [4].

TABLE 1.1 Regulatory sections of Part 211—current good manufacturing practice for finished pharmaceuticals

211.1	Scope
211.3	Definitions
211.22	Responsibilities of quality control unit
211.25	Personnel qualifications
211.28	Personnel responsibilities
211.34	Consultants
211.42	Design and construction features
211.44	Lighting
211.46	Ventilation, air filtration, air heating and cooling
211.48	Plumbing
211.50	Sewage and refuse
211.52	Washing and toilet facilities
211.56	Sanitation
211.58	Maintenance
211.63	Equipment design, size, and location
211.65	Equipment construction
211.67	Equipment cleaning and maintenance
211.68	Automatic, mechanical, and electronic equipment
211.72	Filters
211.80	General requirements
211.82	Receipt and storage of untested components, drug product containers, and closures
211.84	Testing and approval or rejection of components, drug product containers, and closures
211.86	Use of approved components, drug product containers, and closures
211.87	Retesting of approved components, drug product containers, and closures
211.89	Rejected components, drug product containers, and closures
211.94	Drug product containers and closures
211.100	Written procedures; deviations
211.101	Charge-in of components
211.103	Calculation of yield
211.105	Equipment identification
211.110	Sampling and testing of in-process materials and drug products
211.111	Time limitations on production
211.113	Control of microbiological contamination
211.115	Reprocessing
211.122	Materials examination and usage criteria
211.125	Labeling issuance
211.130	Packaging and labeling operations
211.132	Tamper-evident packaging requirements for over-the-counter (OTC) human drug products
211.134	Drug product inspection
211.137	Expiration dating
211.142	Warehousing procedures
211.150	Distribution procedures
211.160	General requirements
211.165	Testing and release for distribution

(*Continued*)

TABLE 1.1 (Cont'd)

211.166	Stability testing
211.167	Special testing requirements
211.170	Reserve samples
211.173	Laboratory animals
211.176	Penicillin contamination
211.180	General requirements
211.182	Equipment cleaning and use log
211.184	Component, drug product container, closure, and labeling records
211.186	Master production and control records
211.188	Batch production and control records
211.192	Production record review
211.194	Laboratory records
211.196	Distribution records
211.198	Complaint files
211.204	Returned drug products
211.208	Drug product salvaging

TABLE 1.2 Regulatory sections of Part 820—quality system regulation

820.1	Scope
820.3	Definitions
820.5	Quality system
820.20	Management responsibility
820.22	Quality audit
820.25	Personnel
820.30	Design controls
820.40	Document controls
820.50	Purchasing controls
820.60	Identification
820.65	Traceability
820.70	Production and process controls
820.72	Inspection, measuring, and test equipment
820.75	Process validation
820.80	Receiving, in-process, and finished device acceptance
820.86	Acceptance status
820.90	Nonconforming product
820.100	Corrective and preventive action
820.120	Device labeling
820.130	Device packaging
820.140	Handling
820.150	Storage
820.160	Distribution
820.170	Installation
820.180	General requirements
820.181	Device master record
820.184	Device history record
820.186	Quality system record
820.198	Complaint files
820.200	Servicing
820.250	Statistical techniques

If the classification of a product as a drug, device, biological product, or combination product is unclear or in dispute, the sponsor can file a request for designation (RFD) with FDA Office of Combination Products (OCP) in accordance with Part 3 of Title 21 of the Code of Federal Regulations (21 CFR Part 3) to obtain a formal classification determination for the product, as provided for under section 563 of the FD&C Act (21 USC 360bbb-2). In reviewing an RFD, the Agency considers the information provided in the RFD as well as other information available to the Agency at that time. Generally, the Agency will respond in writing within 60 days of the sponsor's RFD filing, identifying the classification of the product as a drug, device, biological product, or combination product. If the Agency does not provide a written response within 60 days, the sponsor's recommendation respecting the classification of the product is considered to be the final determination.

In the United States, FDA's determination of whether to classify a product as a drug or a device is based on the statutory definitions of these terms set forth in sections 201(g) and 201(h) of the FD&C Act, as applied to the scientific data concerning the product that are available to FDA at the time the classification determination is made.

1.2.2.1 Definition of Drug Section 201(g) of the FD&C Act defines the term "drug" as (A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any articles specified in clause (A), (B), or (C).

1.2.2.2 Definition of Device Section 201(h) of the FD&C Act defines the term "device" as …an instrument, apparatus, implement, machine, contrivance, implant, *in vitro* reagent, or other similar or related article, including any component, part, or accessory, which is:

1. recognized in the official National Formulary or the United States Pharmacopeia or any supplement to them,
2. intended for use in the diagnosis of disease or other conditions or in the cure, mitigation, treatment, or prevention of disease in man or other animals, or
3. intended to affect the structure or any function of the body of man or other animals and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.

1.2.3 Center for Biologics Evaluation and Research

Human cells or tissue intended for implantation, transplantation, infusion, or transfer into a human recipient is regulated as a human cell, tissue, and cellular and tissue-based product or HCT/P. CBER regulates HCT/Ps under 21 CFR Parts 1270 and 1271. CBER enforces CGMP through Part 600, 601, and 610 (in addition to GMP Part 211) in Table 1.3, Table 1.4, and Table 1.5. CBER's role includes implementation of

TABLE 1.3 Regulatory sections of Part 600—biological products: general

600.2	Mailing addresses
600.3	Definitions
600.10	Personnel
600.11	Physical establishment, equipment, animals, and care
600.12	Records
600.13	Retention samples
600.14	Reporting of biological product deviations by licensed manufacturers
600.15	Temperatures during shipment
600.20	Inspectors
600.21	Time of inspection
600.22	Duties of inspector
600.80	Postmarketing reporting of adverse experiences
600.81	Distribution reports
600.90	Waivers

TABLE 1.4 Regulatory sections of Part 601—biologic license application

601.2	Applications for biologics licenses; procedures for filing
601.3	Complete response letter to the applicant
601.4	Issuance and denial of license
601.5	Revocation of license
601.6	Suspension of license
601.7	Procedure for hearings
601.8	Publication of revocation
601.9	Licenses; reissuance
601.12	Changes to an approved application
601.14	Regulatory submissions in electronic format
601.15	Foreign establishments and products: samples for each importation
601.20	Biologics licenses; issuance and conditions
601.21	Products under development
601.22	Products in short supply; initial manufacturing at other than licensed location
601.25	Review procedures to determine that licensed biological products are safe, effective, and not misbranded under prescribed, recommended, or suggested conditions of use
601.26	Reclassification procedures to determine that licensed biological products are safe, effective, and not misbranded under prescribed, recommended, or suggested conditions of use
601.27	Pediatric studies
601.28	Annual reports of postmarketing pediatric studies
601.29	Guidance documents
601.30–601.36	Diagnostic radiopharmaceuticals
601.30	Scope
601.31	Definition
601.32	General factors relevant to safety and effectiveness
601.33	Indications
601.34	Evaluation of effectiveness

(*Continued*)

TABLE 1.4 (Cont'd)

601.35	Evaluation of safety
601.40–601.46	Accelerated approval of biological products for serious or life-threatening illnesses
601.40	Scope
601.41	Approval based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity
601.42	Approval with restrictions to assure safe use
601.43	Withdrawal procedures
601.44	Postmarketing safety reporting
601.45	Promotional materials
601.46	Termination of requirements
601.50	Confidentiality of data and information in an investigational new drug notice for a biological product
601.51	Confidentiality of data and information in applications for biologics licenses
601.70	Annual progress reports of postmarketing studies
601.90–601.95	Approval of biological products when human efficacy studies are not ethical or feasible
601.90	Scope
601.91	Approval based on evidence of effectiveness from studies in animals
601.92	Withdrawal procedures
601.93	Postmarketing safety reporting
601.94	Promotional materials
601.95	Termination of requirements

TABLE 1.5 Regulatory sections of Part 610—general biological product standards

610.1	Tests prior to release required for each lot
610.2	Requests for samples and protocols; official release
610.9	Equivalent methods and processes
610.10	Potency
610.11	General safety
610.11a	Inactivated influenza vaccine, general safety test
610.12	Sterility
610.13	Purity
610.14	Identity
610.15	Constituent materials
610.16	Total solids in serums
610.17	Permissible combinations
610.18	Cultures
610.20	Standard preparations
610.21	Limits of potency
610.30	Test for *mycoplasma*
610.40	Test requirements
610.41	Donor deferral
610.42	Restrictions on use for further manufacture of medical devices
610.44	Use of reference panels by manufacturers of test kits

(*Continued*)

TABLE 1.5 (Cont'd)

610.46	Human immunodeficiency virus (HIV) "lookback" requirements
610.47	Hepatitis C virus (HCV) "lookback" requirements
610.48	Hepatitis C virus (HCV) "lookback" requirements based on review of historical testing records
610.50	Date of manufacture
610.53	Dating periods for licensed biological products
610.60	Container label
610.61	Package label
610.62	Proper name; package label; legible type
610.63	Divided manufacturing responsibility to be shown
610.64	Name and address of distributor
610.65	Products for export
610.67	Barcode label requirements
610.68	Exceptions or alternatives to labeling requirements for biological products held by the strategic national stockpile

the regulation of preventive and therapeutic vaccines, blood and blood products, human cell and tissue-based products, gene therapies, and xenotransplantation (a procedure that uses a different species as a source of transplanted materials) [5].

No lot of any licensed product shall be released by the manufacturer prior to the completion of tests for conformity with standards applicable to such a product, which include tests for potency, sterility, purity, and identity (21 CFR Part 610, Subpart B). These requirements apply to all biological products, including autologous and single-patient allogeneic products, where a lot may be defined as a single dose.

Some Cellular and Gene Therapy (CGT) products may also contain, in addition to the active ingredient, one or more substances commonly referred to in the scientific literature as an "adjuvant." An adjuvant shall not be introduced into a product unless there is satisfactory evidence that it does not affect adversely the safety or potency of the product (21 CFR 610.15(a)).

Some of the challenges in the development of CGT products include the variability and complexity inherent in the components used to generate the final product, such as the source of cells (i.e., autologous or allogeneic), the potential for adventitious agent contamination, the need for aseptic processing, and the inability to "sterilize" the final product because it contains living cells. Distribution of these products can also be a challenge due to stability issues and the frequently short dating period of many cellular products, which may necessitate release of the final product for administration to a patient before certain test results are available.

1.2.4 Regulatory Submission Requirement

Each therapeutic delivery solution in the United States is regulated by different centers as mentioned earlier. Table 1.6 gives the summary of the regulating center and the documents that need to be filed for investigation and marketing.

TABLE 1.6 Summary of application type and designated regulating center

	Application type	Purpose	Regulating center
Clinical trials approval	IDE (investigation device exemption)	Approval to begin clinical evaluation of a device	CDRH
	IND (investigational new drug)	Approval to begin clinical evaluation of a drug	CDER or CBER (if biological drug)
Approval to market for a medical device or drug	PMA (premarket approval)	Permission to market a new medical device	CDRH
	510(k)	Premarket notification for a medical device substantially equivalent to an already marketed device	CDRH
	NDA (new drug application)	Permission to market a new drug	CDER
	ANDA (abbreviated (new drug application)	Permission to market a generic version of a drug comparable to an innovator drug product (already approved in the USA) in dosage form, strength, route of administration, quality, performance characteristics, and intended use.	CDER
	505 (b)(2)	Permission to market a drug product relying in part on data from existing reference drugs	CDER
	BLA (biologic license application)	Permission to market a new biologic drug	CBER

1.2.4.1 Small Molecule and Macromolecule Submission Both small molecule and macromolecule drugs are under the jurisdiction of CDER and CBER respectively. Both classes of drugs will go through similar IND and new drug application (NDA) processes from its development to marketing. Generic drugs will go through the abbreviated new drug application (ANDA) process.

1.2.4.2 Medical Devices Medical devices are classified into Class I, II, and III based upon the risk they are considered to present with the required level of regulatory control increasing from Class I to Class III.

Most Class I devices do not require premarket notification or approval and so are just subject to General Controls. Most Class II devices require Premarket Notification through a 510(k) process. Most Class III devices require Premarket Approval, for example, through the premarket approval (PMA) process. Device classification depends on the intended use of the device as well as its indications for use.

The FDA has classified around 1700 generic types of device which are grouped into 16 medical specialities or panels. Classification information is provided in a freely accessible database.

A device manufacturer can also request classification by the FDA. If the FDA concludes that the device is not substantially equivalent to a predicate device, then it will be designated as Class III unless the device manufacturer makes a de novo petition requesting the FDA to make a risk-based classification determination for the device. If the FDA grants the de novo petition, then the device will be reclassified from Class III to class II or I.

1.2.4.3 Medical Device 510(k) Premarket Notification Some drug delivery devices aimed for general use are regulated as medical devices. For example, an autoinjector could be approved as a Class II device by the 510(k) route and then utilized with different drugs, each of which would be subject to its own submission as a combination product. But the fact that the autoinjector already has 510(k) approval should reduce the burden of review for the combination product.

This is the main route of approval for Class II devices and is based on showing that a new device is substantially equivalent to a predicate device, that is, that it is at least as safe and effective as an already marketed device.

1.2.4.4 Medical Device Premarket Approval (PMA) This is an FDA route for approval for Class III devices and involves a detailed scientific and regulatory review to evaluate the safety and effectiveness of the device. Given the greater depth of review, the period is 180 days, although in practice, the review period can be much longer due to the need to provide additional information to the FDA. The process also requires Quality System Regulation (QSR) inspection prior to product approval and launch.

1.2.4.5 Medical Device Quality System Regulation Class II and III device manufacturers need to comply with Quality System Regulation 21 CFR 820 (see Table 1.2 for summary). This is based on an early version of ISO 9001 (1994) with additional requirements for design and process validation and transfer.

1.2.5 FDA Compliance Program

FDA Compliance Programs are set up to provide instructions to FDA personnel for conducting activities to evaluate industry compliance with the FD&C Act and other

laws administered by FDA [6]. These compliance programs neither create nor confer any rights for, or on, any person and do not operate to bind FDA or the public. Alternative approaches may be used as long as they satisfy the requirements of applicable statutes and regulations.

FDA Compliance Programs are organized by the following program areas:

- Biologics (CBER)
- Bioresearch Monitoring (BIMO)
- Devices/Radiological Health (CDRH)
- Drugs (CDER)
- Food and Cosmetics (CFSAN)
- Veterinary Medicine (CVM)

Compliance programs that affect the three therapeutic areas in CBER, BIMO, CDRH, and CDER are tabulated in Table 1.7, Table 1.8, Table 1.9, and Table 1.10.

TABLE 1.7 Compliance programs of CBER

Program no.	CBER compliance program title
7341.002	Inspection of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)
7341.002A	Inspection of tissue establishments (covers human tissue recovered before 5/25/2005)
7342.001	Inspection of licensed and unlicensed blood banks, brokers, reference laboratories, and contractors
7342.002	Inspection of source plasma establishments, brokers, testing laboratories, and contractors
7342.007	Imported CBER-regulated products
7342.008	Inspection of licensed *in vitro* diagnostic (IVD) devices regulated by CBER
7345.848	Inspection of biological drug products (PDF—570 kb) Replaces 7342.006—inspection of plasma derivatives of human origin, 7345.001—inspection of licensed allergenic products, 7345.002—inspection of licensed vaccines

TABLE 1.8 Compliance program in BIMO

Program no.	BIMO compliance program title
7348.001	*In vivo* bioequivalence
7348.808	Good laboratory practice (nonclinical laboratories)
7348.808A	Good laboratory practice program (nonclinical laboratories) EPA data audit inspections
7348.809	Institutional review board
7348.809A	Radioactive drug research committee
7348.810	Sponsors, contract research organizations, and monitors
7348.811	Clinical investigators

TABLE 1.9 Compliance program in CDRH

Program no.	CDRH compliance program title
7382.845	Inspection of medical device manufacturers
7383.001	Medical device premarket approval and postmarket inspections
7385.014	Mammography facility inspections
7386.001	Inspection and field testing of radiation-emitting electronic products
7386.003	Field compliance testing of diagnostic medical X-ray equipment Attachments A-M
7386.003a	Inspection of domestic and foreign manufacturers of diagnostic X-ray equipment
7386.006	Compliance testing of electronic products at WEAC
7386.007	Imported electronic product
7386.008	Medical device and radiological health use control and policy implementation
7386.009	Emergency planning and response activities: Part VI

TABLE 1.10 CDER compliance program

Program no.	CDER compliance program title
7348.001	*In vivo* bioequivalence
7348.809A	Radioactive drug research committee
7346.832	Preapproval inspections/investigations
7346.843	Postapproval audit inspections
7352.002	Unapproved new drugs (marketed, human, prescription drugs only)
7352.004	*In vitro* method development and validation for generic drugs
7353.001	Postmarketing adverse drug experience (PADE) reporting inspections
7356.002	Drug manufacturing inspections
7356.002A	Sterile drug process inspections
7356.002B	Drug repackers and relabelers
7356.002C	Radioactive drugs
7356.002E	Compressed medical gases
7356.002F	Active pharmaceutical ingredients
7356.002M	Inspections of licensed biological therapeutic drug products
7356.002P	Positron emission tomography
7356.008	Drug quality sampling and testing—human drugs
7356.014	Drug listing
7356.014A	Drug listing—labeling review
7356.020	Compendial monograph evaluation and development (CMED)
7356.020A	Compendial method assessment
7356.021	Drug quality reporting system (DQRS) (MedWatch reports) NDA field alert reporting (FAR)
7356.022	Enforcement of the prescription drug marketing act (PDMA)
7361.003	OTC drug monograph implementation
7363.001	Fraudulent drugs