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

Therapeutic Delivery Solutions, First Edition. Edited by Chung Chow Chan, Kwok Chow, Bill McKay, and Michelle Fung.

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

1.3 INITIATIVES IN THE PHARMACEUTICAL, MEDICAL DEVICE, AND CELL THERAPY REGULATORY REQUIREMENTS

In recent years, threats from adulteration (including economically motivated adulteration) of medical products is real. The consequences, throughout the world, have been tragic: Glycerin used in the manufacture of fever medicine and cough syrup and teething products was adulterated with diethylene glycol (DEG) resulting in the deaths of children in Haiti, Panama, and Nigeria. In 2007, pet food adulterated with the industrial chemical melamine sickened several thousand pets in the United States. That same contaminant was added to infant formula in China, fatally poisoning six babies in China and making 300,000 others gravely ill. In 2008, heparin contamination crisis in the United States was associated with several deaths and cases of serious illness.

FDA and other global regulatory agencies are playing an increasingly integral role, not just dedicated to ensuring safe and effective products, but also to promote public health and participate more actively in the scientific research enterprise directed toward new treatments and interventions. The global regulatory agencies are also modernizing its evaluation and approval processes by utilizing regulatory science to ensure that innovative products reach the patients who need them, when they need them.

Regulatory science is defined as the science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of regulated products. Regulatory science is the foundation of FDA decision-making. Both the knowledge generated in developing new tools and the tools themselves have the potential to inform a broad range of health-related advances, involving numerous diseases and conditions. For example, a project to explore how to characterize and predict undesired immune responses that can alter or block the effects of recombinant proteins and monoclonal antibodies can demonstrate relevance to the treatment of cancer, rheumatoid arthritis, and other diseases. The knowledge generated from such studies may well be applicable across entire classes of medical products and could help better ensure that such medicines are both safe and effective.

Regulatory science does not take place only in laboratories. It involves scientific tools and information-gathering and analytical systems to study data, people, health systems, and communities. To be most effective, advances in regulatory science must be fully integrated into the entire product development process.

Outreach and collaborative efforts are integral to predicting the failure or success of new discoveries and technologies early in development and reducing product development costs. Advances in regulatory science will help make the evaluation and approval process more efficient, helping to deliver safe new products to patients faster and strengthening the ability to monitor product use and improve performance, thus enhancing patient outcomes.

To successfully achieve the mission to promote and protect the public health requires a right balance between innovation and safety. Regulatory science should

not stifle innovation, but rather encourage innovation while maintaining a commitment to safety and effectiveness.

The Chemistry, Control, and Manufacturing issues faced by the development of pharmaceutical, medical device, and cell therapy delivery solutions are similar philosophically. The pharmaceutical and cell therapy deliveries follow more similar regulatory interpretation. However, unlike a drug whose active ingredient does not change and whose inherent flaws cannot generally be fixed, a device can be improved through changes to its design or composition at any time. As a result, regulatory initiatives and review processes of a medical device will follow a similar philosophy but will differ in detail and implementation.

1.3.1 FDA Initiative in Pharmaceutical and Cell Therapy Delivery

Biomedical research has dramatically expanded the understanding of biology and disease. However, the development of new therapies is in decline, and the cost of bringing them to market has increased significantly. Every opportunity to improve the effectiveness and outcomes of healthcare and address growing threats to the strength and innovation of the biotechnology industry ensures that the best medical treatments are made available to patients in a timely manner. The following are some of the challenges and initiatives taken by FDA to modernize product development to improve the speed, efficiency, predictability, capacity, and quality, from development to manufacturing.

1.3.1.1 Expedited Programs for Serious Conditions Speeding the development and availability of drugs that treat serious diseases are in everyone's interest, especially when the drugs are the first available treatment or have advantages over existing treatments. FDA has developed four programs to making such drugs available as rapidly as possible: Fast Track, Breakthrough Therapy, Accelerated Approval, and Priority Review [7].

The following summary describes each program, how they differ, and how they complement each other:

Fast track Fast track is a process designed to facilitate the development and expedite the review of drugs to treat serious conditions and fill an unmet medical need. The purpose is to get important new drugs to the patient earlier. Fast Track addresses a broad range of serious conditions.

Determining whether a condition is serious is a matter of judgment, but generally is based on whether the drug will have an impact on such factors as survival, day-to-day functioning, or the likelihood that the condition, if left untreated, will progress from a less severe condition to a more serious one. AIDS, Alzheimer's, heart failure, and cancer are obvious examples of serious conditions. However, diseases such as epilepsy, depression, and diabetes are also considered to be serious conditions.

Filling an unmet medical need is defined as providing a therapy where none exists or providing a therapy that may be potentially better than available therapy.

Any drug being developed to treat or prevent a condition with no current therapy obviously is directed at an unmet need. If there are available therapies, a fast track drug must show some advantage over available therapy, such as:

- Showing superior effectiveness, effect on serious outcomes, or improved effect on serious outcomes
- Avoiding serious side effects of an available therapy
- Improving the diagnosis of a serious condition where early diagnosis results in an improved outcome
- Decreasing the clinically significant toxicity of an available therapy that is common and causes discontinuation of treatment
- Ability to address emerging or anticipated public health needs

A drug that receives Fast Track designation is eligible for some or all of the following:

- More frequent meetings with FDA to discuss the drug's development plan and ensure collection of appropriate data needed to support drug approval
- More frequent written correspondence from FDA about such things as the design of the proposed clinical trials and use of biomarkers
- Eligibility for Accelerated Approval and Priority Review, if relevant criteria are met
- Rolling Review, which means that a drug company can submit completed sections of its Biological License Application (BLA) or New Drug Application (NDA) for review by FDA, rather than waiting until every section of the application is completed before the entire application can be reviewed. BLA or NDA review usually does not begin until the drug company has submitted the entire application to the FDA

Fast Track designation must be requested by the drug company. The request can be initiated at any time during the drug development process. FDA will review the request and make a decision within 60 days based on whether the drug fills an unmet medical need in a serious condition.

Once a drug receives Fast Track designation, early and frequent communication between the FDA and a drug company is encouraged throughout the entire drug development and review process. The frequency of communication assures that questions and issues are resolved quickly, often leading to earlier drug approval and access by patients.

Breakthrough therapy Breakthrough Therapy designation is a process designed to expedite the development and review of drugs that are intended to treat a serious condition, and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint(s).

To determine whether the improvement over available therapy is substantial is a matter of judgment and depends on both the magnitude of the treatment effect, which

could include duration of the effect, and the importance of the observed clinical outcome. In general, the preliminary clinical evidence should show a clear advantage over available therapy.

For purposes of Breakthrough Therapy designation, clinically significant endpoint generally refers to an endpoint that measures an effect on irreversible morbidity or mortality (IMM) or on symptoms that represent serious consequences of the disease. A clinically significant endpoint can also refer to findings that suggest an effect on IMM or serious symptoms, including:

- An effect on an established surrogate endpoint
- An effect on a surrogate endpoint or intermediate clinical endpoint considered reasonably likely to predict a clinical benefit (i.e., the accelerated approval standard)
- An effect on a pharmacodynamic biomarker(s) that does not meet criteria for an acceptable surrogate endpoint, but strongly suggests the potential for a clinically meaningful effect on the underlying disease
- A significantly improved safety profile compared to available therapy (e.g., less dose-limiting toxicity for an oncology agent), with evidence of similar efficacy

A drug that receives Breakthrough Therapy designation is eligible for the following:

- All Fast Track designation features
- Intensive guidance on an efficient drug development program, beginning as early as Phase 1
- Organizational commitment involving senior managers

Breakthrough Therapy designation is requested by the drug company. If a sponsor has not requested breakthrough therapy designation, FDA may suggest that the sponsor consider submitting a request if (1) after reviewing submitted data and information (including preliminary clinical evidence), the Agency thinks the drug development program may meet the criteria for Breakthrough Therapy designation and (2) the remaining drug development program can benefit from the designation.

Ideally, a Breakthrough Therapy designation request should be received by FDA no later than the end-of-phase-2 meetings if any of the features of the designation are to be obtained. Because the primary intent of Breakthrough Therapy designation is to develop evidence needed to support approval as efficiently as possible, FDA does not anticipate that Breakthrough Therapy designation requests will be made after the submission of an original BLA or NDA or a supplement. FDA will respond to Breakthrough Therapy designation requests within 60 days of receipt of the request.

Accelerated approval When studying a new drug, it can sometimes take many years to learn whether a drug actually provides a real effect on how a patient survives, feels, or functions. A positive therapeutic effect that is clinically meaningful in the context of a given disease is known as “clinical benefit.” It may take an extended

period of time to measure a drug's intended clinical benefit. Therefore, in 1992 FDA instituted the Accelerated Approval regulations to allow drugs for serious conditions that filled an unmet medical need to be approved based on a surrogate endpoint. Using a surrogate endpoint enabled the FDA to approve these drugs faster.

Section 901 of the Food and Drug Administration Safety Innovations Act (FDASIA) in 1992 amended the Federal Food, Drug, and Cosmetic Act (FD&C Act) to allow the FDA to base accelerated approval for drugs for serious conditions that fill an unmet medical need on whether the drug has an effect on a surrogate or an intermediate clinical endpoint.

A surrogate endpoint used for accelerated approval is a marker—a laboratory measurement, radiographic image, physical sign, or other measure that is thought to predict clinical benefit, but is not itself a measure of clinical benefit. Likewise, an intermediate clinical endpoint is a measure of a therapeutic effect that is considered reasonably likely to predict the clinical benefit of a drug, such as an effect on irreversible morbidity and mortality (IMM).

The FDA bases its decision on whether to accept the proposed surrogate or intermediate clinical endpoint on the scientific support for that endpoint. Studies that demonstrate a drug's effect on a surrogate or intermediate clinical endpoint must be "adequate and well controlled" as required by the FD&C Act.

Using surrogate or intermediate clinical endpoints can save valuable time in the drug approval process. For example, instead of having to wait to learn if a drug actually extends survival for cancer patients, the FDA may approve a drug based on evidence that the drug shrinks tumors, because tumor shrinkage is considered reasonably likely to predict a real clinical benefit. In this example, an approval based upon tumor shrinkage can occur far sooner than waiting to learn whether patients actually lived longer. The drug company will still need to conduct studies to confirm that tumor shrinkage actually predicts that patients will live longer. These studies are known as Phase 4 confirmatory trials.

Where confirmatory trials verify clinical benefit, FDA will generally terminate the requirement. Approval of a drug may be withdrawn or the labeled indication of the drug changed if trials fail to verify clinical benefit or do not demonstrate sufficient clinical benefit to justify the risks associated with the drug (e.g., show a significantly smaller magnitude or duration of benefit than was anticipated based on the observed effect on the surrogate).

Priority review Prior to approval, each drug marketed in the United States must go through a detailed FDA review process. In 1992, under the Prescription Drug User Act (PDUFA), FDA agreed to specific goals for improving the drug review time and created a two-tiered system of review times—Standard Review and Priority Review. A Priority Review designation means FDA's goal is to take action on an application within 6 months (compared to 10 months under standard review).

A Priority Review designation will direct overall attention and resources to the evaluation of applications for drugs that, if approved, would be significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions when compared to standard applications.

Significant improvement may be demonstrated by the following examples:

- Evidence of increased effectiveness in treatment, prevention, or diagnosis of conditions
- Elimination or substantial reduction of a treatment-limiting drug reaction
- Documented enhancement of patient compliance that is expected to lead to an improvement in serious outcomes
- Evidence of safety and effectiveness in a new subpopulation

FDA decides on the review designation for every application. However, an applicant may expressly request priority review as described in the Guidance for Industry Expedited Programs for Serious Conditions—Drugs and Biologics. It does not affect the length of the clinical trial period. FDA informs the applicant of a Priority Review designation within 60 days of the receipt of the original BLA, NDA, or efficacy supplement. Designation of a drug as "Priority" does not alter the scientific/medical standard for approval or the quality of evidence necessary.

Fast Track, Breakthrough Therapy, Accelerated Approval, and Priority Review are approaches intended to make therapeutically important drugs available at an earlier time. They do not compromise the standards for the safety and effectiveness of the drugs that become available through this process.

1.3.1.2 Greater Availability of Generic Drugs Generic drugs make up more than 70% of the prescriptions filled in the United States as well as other countries in the world and usually is the only solution to affordable treatment. However, many products do not have generic alternatives even though patents for the reference products have expired. More generic products could be made available if the difficulty in determining bioequivalence for some products could be overcome. Metered-dose inhalers, dry-powder inhalers, certain topical products, and products that are not systemically absorbed present challenges in determining bioequivalence. Developing validated methods for determining bioequivalence for these products so that quality, lower-cost generic products can become more widely available are being pursued.

Generic Drug User Fee Amendments of 2012 (GDUFA) provides user fees for FDA to ensure timely review of applications for generic drugs. GDUFA is designed to speed access to safe and effective generic drugs to the public and reduce costs to industry. The law requires industry to pay user fees to supplement the costs of reviewing generic drug applications and inspecting facilities. Additional resources enable FDA to reduce backlog of pending applications, cut the average time required to review generic drug applications for safety, and increase risk-based inspections.

GDUFA is built on the success of the Prescription Drug User Fee Act (PDUFA). Over the past 20 years, PDUFA has ensured a more predictable, consistent, and streamlined premarket program for industry and helped speed access to new, safe, and effective prescription drugs for patients. GDUFA will also enhance global supply chain safety by requiring that generic drug facilities and sites around the world self-identify.

The GDUFA Regulatory Science Plan had identified 13 research topics for further study and ranged from quality-by-design (QbD) and postmarketing surveillance to bioequivalence (BE) and pharmacokinetic (PK) evaluation of complex dosage forms [8].

FDA had also issued draft guidances on developing and approving biosimilars, using a risk-based "totality-of-the-evidence" approach. The guidance to industry is contained in three documents and represents FDA's interpretation of the Biologics Price Competition and Innovation Act of 2009 (BPCI Act), which creates an abbreviated licensure pathway for biological products shown to be biosimilar to or interchangeable with an FDA-licensed biological reference product and was part of the Patient Protection and Affordable Care Act.

The first document, "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product," explains the evaluation approach, intended to help companies submitting new 351(k) applications for demonstrating biosimilarity. This document includes recommendation for a gradual or "stepwise" approach in the development of biosimilar products, which include a comparison of the proposed product and the reference product with respect to structure, function, animal toxicity, human pharmacokinetics (PK) and pharmacodynamics (PD), clinical immunogenicity, and clinical safety and effectiveness.

Once a product is determined to be biosimilar, it will be eligible for a separate interchangeability determination. To meet the higher standard of "interchangeability," an applicant must provide sufficient information to demonstrate biosimilarity and also to demonstrate that the biological product can be expected to produce the same clinical result as the reference product in any given patient. Interchangeable products may be substituted for the reference product without the intervention of the prescribing healthcare provider.

The second draft guidance document, "Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product," provides an overview of analytical factors for drug developers to consider when assessing biosimilarity between a proposed therapeutic protein product and a reference product. Those factors include the expression system, the manufacturing process, an assessment of physicochemical properties, functional activities, receptor binding and immunochemical properties, impurities, the reference product and reference standards, and stability. This guidance expects that the expression construct for a proposed biosimilar product will encode the same primary amino acid sequence as its reference product.

The third guidance document, "Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation (BPCI) Act of 2009," answers common questions about biosimilar product development in a question-and-answer format. Questions are intended to address concerns arising in the early stages of product development, including requesting meetings with the FDA, addressing differences in formulation from the reference product, and requesting exclusivity.

Once applications are received for approval of a biosimilar drug, FDA has committed to reviewing them within 10 months under the fifth authorization of the Prescription Drug User Fee Act (PDUFA).

The BPCI Act also includes:

- A 12-year exclusivity period from the date of first licensure of the reference product, during which approval of a 351(k) application referencing that product may not be made effective
- A 4-year exclusivity period from the date of first licensure of the reference product, during which a 351(k) application referencing that product may not be submitted
- An exclusivity period for the first biological product determined to be interchangeable with the reference product for any condition of use, during which a second or subsequent biological product may not be determined interchangeable with that reference product

1.3.1.3 Other Product Development Initiatives

Modernized manufacturing and product quality FDA and other global regulatory agencies are leading efforts on "Quality by Design (QbD)," which applies regulatory science to modernize the understanding and control of medical product manufacturing processes. Advances in regulatory science will not only ensure better quality, but could also lower development and manufacturing costs. In the United States, areas of investigation supported by FDA include (1) continuous processing, in which materials constantly flow in and out of the equipment and reduce overall manufacturing time and cost; (2) the use of process analytical technology (PAT) to monitor and control manufacturing processes as opposed to just testing products; and (3) new statistical approaches to detect changes in process or product quality. Applying these approaches will help control complex manufacturing processes, enhance their efficiency, and provide more reliable products to patients. In addition, new technologies such as flexible manufacturing facilities and the use of modular and disposable equipment can speed production of products in routine and emergency situations.

National Vaccine Plan The National Vaccine Plan was initially created in 1994 to provide a strategic approach for maximizing the impact of vaccines on the health of U.S. populations [9]. In 2010, the National Vaccine Plan was updated to reflect the priorities, opportunities, and challenges of today's science and the national immunization program, and it provides a guiding vision for vaccines and immunization in the United States for the decade 2010–2020 with the following five goals.

Goal 1: Develop new and improved vaccines.

Goal 2: Enhance the vaccine safety system.

Goal 3: Support communications to enhance informed vaccine decision-making.

Goal 4: Ensure a stable supply of, access to, and better use of recommended vaccines in the United States.

Goal 5: Increase global prevention of death and disease through safe and effective vaccination.

Two areas to note in the development of new and improved vaccines are as follows.

Development of the next generation of influenza vaccines Scientists at NIH's National Institute of Allergy and Infectious Diseases (NIAID) have recently devised a new strategy for the development of more broadly protective vaccines for influenza, an approach that represents a promising step forward toward a universal influenza vaccine. Since influenza viruses change rapidly, influenza vaccines are updated and produced annually to protect against the virus strains that will be most common that year. In animal studies, researchers at NIH/NIAID were able to elicit an immune response to sites within influenza viruses that are shared across different influenza strains and that typically do not change very much over time, despite ongoing mutations in the virus. This is one of the many strategies toward the development of a safe and effective universal influenza vaccine, which would potentially eliminate the need for a new seasonal influenza vaccine each year and could remove the threat of an influenza pandemic.

SMART Vaccines As technological opportunities emerge and patterns of disease change over time, it is difficult to decide how best to invest in new vaccine development and introduce new vaccines into routine and campaign immunization programs. In 2012, the Institute of Medicine (IOM), with National Vaccine Program Office (NVPO), began developing a decision support tool for prioritizing vaccine targets for development and use. They developed a software called Strategic Multi-Attribute Ranking Tool for Vaccines (SMART Vaccines).

The SMART Vaccines software makes it possible for decision-makers to develop and test hypotheses and assumptions, weigh competing values, and explore alternative scenarios and vaccine attributes to assist in setting priorities for vaccine targets for development and introduction. Users can take into account multiple factors, including health, economic, demographic, scientific, and policy considerations and can assess their relative rank among a range of factors. The tool allows the flexibility of factoring in values such as aiming to eradicate or eliminate a disease. Users are also able to generate information on cost-effectiveness, premature deaths averted, and gains in worker productivity, among other topics of importance to vaccine development and introduction. Using this model, SMART Vaccines has the potential not only to guide discussions regarding vaccine goals but also to provide a common platform for determining priority areas of national and global interests. The SMART Vaccines software is now available to the public for download and use online through the National Academy of Sciences website at http://www.nap.edu/smartvaccines.

New approaches to evaluate product efficacy in vaccine It is not always possible to test whether a vaccine or treatment will work against a new or emerging infectious disease or against a terrorist threat because the threat may be rare or even nonexistent at the time the therapy needs to be developed. Animal testing is often the only available option, but many diseases lack good animal models, and animal studies are technically difficult to conduct and typically limited in size. Therefore, regulatory

science will help to develop and validate improved predictive models. Regulatory science can also support the identification and validation of surrogate measures of product efficacy. For example, FDA's definition and acceptance of a serum hemagglutination inhibition antibody titer, which helps predict the efficacy of influenza vaccines, took years off the time required to approve new flu vaccines and, as a result, helped to double the number and capacity of U.S. licensed flu vaccine makers. Such biomarkers (e.g., responses in blood tests and other measurements or medical images) that predict efficacy are not yet available for most terrorism threats, emerging pathogens, or major global infectious diseases. Efforts to develop, refine, and validate new biomarkers can lower development costs and improve and speed the development of safe and effective products for unmet public health needs.

More flexible and agile approaches to product development and manufacturing of vaccines and biotech products Knowledge of genetic sequences enable production of DNA and recombinant vaccines or needed treatments and diagnostic tests more quickly and safely without using the pathogen in manufacturing.

The use of platform technologies of this sort may offer the potential to scale up production more rapidly. For example, several technologies could potentially allow production of large amounts of new influenza vaccines for a pandemic in weeks rather than months. Platform technologies may also be applicable across broader ranges of products. For example, the same virus-like particle, live vector, DNA vaccine, or recombinant protein expression system could be used as the basis to rapidly develop and produce different, distinct vaccines intended to protect against illnesses such as flu, plague, SARS, or TB. Even stronger commonalities apply across technologies that can be used for detection or diagnosis, such as high-throughput assays for antibody, antigen, and nucleic acid detection.

Regulatory science helps to evaluate multiuse technologies and products including new methodologies for measuring product quality, potency, safety, and effectiveness.

1.3.2 Initiative of the Medical Device Delivery System

There has been a lot of discussion about balancing innovation and safety—whether there is a need to have more regulation of medical devices to assure safety and effectiveness—or whether there is a need to have less regulation of medical devices to foster innovation. In the United States, the FDA's medical device initiative, Innovation Pathway, establishes how innovation and safety and effectiveness do not have to exist on opposite ends of a swinging pendulum. They can be complementary and mutually supporting.

1.3.2.1 Expedited Access Premarket Approval Application for Unmet Medical Needs for Life Threatening or Irreversibly Debilitating Diseases or Conditions ("Expedited Access PMA" or "EAP") Program The program features earlier and more interactive engagement with FDA staff—including the involvement of senior management and a collaboratively developed plan for collecting the scientific and clinical data to support approval [10a].

To be eligible for participation in the program, the medical device must fulfill the following criteria:

- Be intended to treat or diagnose a life-threatening or irreversibly debilitating disease or condition
- Represent one of the following:
  1. no approved alternative treatment/diagnostic exists, or
  2. a breakthrough technology that provides a clinically meaningful advantage over existing technology, or
  3. offers a significant, clinically meaningful advantage over existing approved alternatives, or
  4. availability is in the patient's best interest
- Have an acceptable data development plan that has been approved by the FDA

The EAP builds on the Innovation Pathway pilot, which is described in the following, and the FDA's experience with expedited review programs for pharmaceuticals, including Accelerated Approval and Breakthrough Therapies.

In addition to the EAP, a separate draft guidance is published that outlines FDA's current policy on when data can be collected after product approval and what actions are available to the FDA if approval conditions, such as postmarket data collection, are not met. Also included in the guidance is advice on the use of surrogate or independent markers to support approval, similar to the data points used for accelerated approval of prescription drugs [10b].

1.3.2.2 Innovation Pathway The goal of Innovation Pathway is to reduce the overall time and cost it takes for the development, assessment, and review of safe and effective medical devices that address unmet medical needs so these devices can get to the patients who need them sooner without jeopardizing patient safety. It will promote high-quality regulatory science and help FDA better prepare and respond to transformative technologies and scientific breakthroughs [10c].

Innovation Pathway will be developing and rapidly testing new approaches to premarket review including the use of a decision support tool that will help assure that the regulatory decisions are more transparent and consistent. Such a tool can help decide whether there is sufficient evidence to allow the device to be studied for the first time in humans. An example of the Initiative Pathway is its application to products for patients with end stage renal disease—ESRD.

Because these are novel technologies, it is likely to raise new scientific and regulatory challenges. Key features of this pathway will be identifying and resolving these issues early by leveraging scientific expertise outside of the agency from the Network of Experts.

Clinical trial protocols would be developed by the sponsor and CDRH through an interactive process and have flexibility built in to allow for repeat testing and redesign.

Front-loading resources will reduce unnecessary delays and review these devices for approval in roughly half the time it takes for the typical premarket approval, or

PMA, application. However, devices that utilize the Innovation Pathway must still adhere to the regulatory standards for new applications. Just because a device is accepted into the pathway does not mean it is destined for approval.

Another initiative by CDRH to strengthen device research is the creation of a voluntary third-party certification program for medical device test centers across the country. Eligible test centers would have expertise in both device design and the conduct of high-quality clinical studies.

Unlike a drug whose active ingredient does not change and whose inherent flaws cannot generally be fixed, a device can be improved through changes to its design or composition at any time. By providing incentives to universities and other institutions in a competitive way to combine expertise in developing and in assessing devices, they can help find and fix problems earlier. Additionally, since certified test centers have well-established safety records, they will be permitted to conduct first-in-human studies at an earlier stage in device development. As a result, the device development process would become more predictable, safer, and less costly.

1.3.2.3 Training of New Regulatory Scientists in Medical Device In the United States and other countries, unlike the pharmaceutical industry, the education system has few programs in the device development. To train future innovators, regulators, academia, industry, and the healthcare community will need to work together to develop a publicly available core curriculum in device design, testing, regulatory processes, and postmarketing surveillance.

1.3.2.4 Acceptability of Data Device manufacturers had been conducting much device research overseas. However, there are difficulties in the United States to accept these data. Clear guidance from the FDA on criteria and circumstances under which data developed overseas could be used to support device submissions will result in better data and less of a need to conduct additional clinical studies. This situation will also provide a smoother review, less cost to companies, and fewer risks to patients from investigational devices.

1.3.2.5 Human Factors and Usability Engineering to Optimize Medical Device Design Human factors engineering (HFE) and usability engineering (UE) is the study to understand and optimize how people interact with technology. HFE/UE are important to the development of medical devices and include three major components of the device-user system: (1) device users, (2) device use environments, and (3) device user interfaces.

The process of eliminating or reducing design-related use problems for medical devices that contribute to or cause unsafe or ineffective medical treatment is part of a process for controlling overall risk. Where harm could result from "use errors," the dynamics of user interaction are safety-related and should be components of risk analysis and risk management.

Medical devices should be designed so that the devices are safe and reliable for their intended uses. To achieve this goal, the possibilities of hazards arising from use of and failures of the device and its components should be evaluated.

Hazards traditionally considered in risk analysis include:

- Chemical hazards (e.g., toxic chemicals)
- Mechanical hazards (e.g., kinetic or potential energy from a moving object)
- Thermal hazards (e.g., high-temperature components)
- Electrical hazards (e.g., electrical shock, electromagnetic interference (EMI))
- Radiation hazards (e.g., ionizing and nonionizing)
- Biological hazards (e.g., allergic reactions, bioincompatibility, and infection)

These hazards most often result from instances of device or component failure that are not dependent on how the user interacts with the device.

In addition, hazards for medical devices that are associated with device use should also be considered and are referred to as use-related hazards. These hazards include use errors involving failure to perceive, read, interpret, or recognize and act on information from monitoring or diagnostic testing devices and improper treatment (e.g., ineffective or dangerous therapy) for devices that provide medical treatment.

Use-related hazards occur for one or more of the following reasons:

- Device use requires physical, perceptual, or cognitive abilities that exceed the abilities of the user.
- The use environment affects operation of the device and this effect is not recognized or understood by the user.
- The particular use environment impairs the user's physical, perceptual, or cognitive capabilities when using the device to an extent that negatively affects the user's interactions with the device.
- Device use is inconsistent with user's expectations or intuition about device operation
- Devices are used in ways that were not anticipated.
- Devices are used in ways that were anticipated but inappropriate and for which adequate controls were not applied.

HFE/UE should be incorporated into device design, development, and risk management processes. Three central steps are essential for performing a successful HFE/UE analysis:

- Identify anticipated use-related hazards and unanticipated use-related hazards and determine how hazardous use situations occur
- Develop and apply strategies to mitigate or control use-related hazards
- Demonstrate safe and effective device use through human factors' validation

From the regulatory perspective, the risk analysis that fulfills Quality System requirements should include use error [11]. To establish the design input for the user interface and carry out design verification, human factors activities conducted throughout the development process can include task/function analyses, user studies, prototype tests, and mock-up reviews. Formative and validation testing fulfill the requirements to test

the device under realistic conditions. Validation testing should be used to demonstrate that the potential for use error has been minimized.

1.4 CURRENT GOOD MANUFACTURING PRACTICE REQUIREMENTS FOR COMBINATION PRODUCTS

The recent breakthrough in science and technology had transformed the ability to treat disease and physiological disorders. As a result, the therapeutic solutions available for a disease state and physiological disorder may have different options available. Using diabetes mellitus as an example, a diabetic patient can be treated using traditional therapy (e.g., antidiabetic oral formulation or subcutaneous insulin), a medical device (insulin pump device), or a combination of a traditional pharmaceutical/medical device and cellular therapy (pancreatic cell transplant). The development efforts of each of these individual aspects are discussed in detail in Chapters 2, 3, 6, 7, 8, and 9. Combination products are getting more commonly used for therapeutic solutions. The regulatory requirements for the combination products are covered from Parts 3 through 1271.

1.4.1 Definition of Combination Products

A combination product is a product comprised of any combination of a drug and a device; a device and a biological product; a biological product and a drug; or a drug, a device, and a biological product. A combination product includes the following:

1. A product comprised of two or more regulated components, that is, drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity (single-entity combination products)
2. Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products (copackaged combination products)
3. A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where, upon approval of the proposed product, the labeling of the approved product would need to be changed, for example, to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose (a type of cross-labeled combination product)
4. Any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect (another type of cross-labeled combination product)

The constituent parts of a combination product retain their regulatory status (as a drug or device, for example) after they are combined. Accordingly, the CGMP requirements that apply to each of the constituent parts continue to apply when they are combined to make combination products.

1.4.2 The Final Rule

The rule offered two options for demonstrating compliance with the CGMP requirements applicable to a copackaged or single-entity combination product [12]. These options were either (1) to demonstrate compliance with the specifics of all CGMP regulations applicable to each of the constituent parts included in the combination product or (2) to demonstrate compliance with the specifics of either the drug CGMPs or the QS regulation, rather than both, when the combination contains both a drug and a device under certain conditions. These conditions included demonstrating compliance with specified provisions from the other of these two sets of CGMP requirements. In addition, for a combination product that included a biological product, the CGMP's requirements for biological products in 21 CFR Parts 600 through 680 would apply, and, for a combination product that included any human cell, tissue, and cellular and tissue-based products (HCT/Ps), the regulations in 21 CFR Part 1271 would apply.

The rule is organized in the four sections addressing scope (Section 4.1), definitions (Section 4.2), the CGMPs that apply to combination products (Section 4.3), and how to comply with these CGMP requirements for a single-entity or copackaged combination product (Section 4.4).

Section 4.1 states that the rule establishes which CGMP requirements apply to combination products, clarifies the application of these requirements, and provides a regulatory framework for designing and implementing CGMP operating systems at facilities that manufacture copackaged or single-entity combination products.

Section 4.2 provides definitions for terms used in the regulation. Some of these definitions are included for convenience, for example, cross-referencing an existing definition (such as for "combination product") or to establish the meaning for a reference term (such as "drug CGMP"). In addition to cross-referencing the definition for "device," the rule states that a device that is a constituent part of a combination product is considered a finished device within the meaning of the QS regulation and also states that a drug that is a constituent part of a combination product is a drug product within the meaning of the drug CGMPs. The definition for "current good manufacturing practice operating system" states that such a system is the operating system within an establishment that is designed and implemented to address and meet the CGMP requirements for a combination product.

Section 4.3 lists all of the requirements that may apply to a combination product under this rule, depending on the types of constituent parts the combination product includes. The CGMP requirements listed are those found in parts 210 and 211 for drugs, part 820 for devices, and parts 600 through 680 for biological products, and the current good tissue practices found in part 1271 for HCT/Ps.

Section 4.4 addresses how to comply with these CGMP requirements for copackaged and single-entity combination products.

The rule helps ensure that CGMP requirements that apply to single-entity and copackaged combination products are clear and consistent, regardless of which component has lead jurisdiction for the combination product or which type of application is submitted for marketing authorization. The rule also streamlines compliance with CGMP requirements for the combination products and to help ensure appropriate implementation of these requirements while avoiding unnecessary redundancy in CGMP operating systems for these products.

1.4.3 Postapproval Modifications to a Combination Product Approved Under a BLA, NDA, or PMA

A draft guidance is available on the underlying principles to determine the type of marketing submission that may be required for postapproval changes to a combination product as defined in 21 CFR 3.2(e) that is approved under one marketing application, that is, a biologic license application (BLA), a new drug application (NDA), or a device premarket approval application (PMA) [13].

The following section gives examples of significant changes that may be made to constituent parts of a combination product (i.e., changes that may require prior approval from FDA). The types of submissions that such changes may require, depending upon the submission type used to obtain approval of the combination product, are identified.

1. Certain changes in the combination product device constituent part (e.g., those that result in a combination product new indication for use, new clinical effects, or in a modified analyte and indication/patient population for an *in vitro* diagnostic) customarily require new preclinical and clinical data to provide support for safety and effectiveness. For any such changes that do not affect the primary mode of action, select the submission type to match the application type used to obtain approval of the combination product:
   a. PMA Original
   b. NDA Original
   c. BLA Original
2. Changes in the drug constituent part substance, drug constituent part production process, quality controls, equipment, or facilities that affect controlled release or drug particle size or have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug constituent part. Such changes include those that may affect the sterility assurance of the drug constituent part, such as process changes for sterile drug substances and sterile packaging components. For such change, select the submission type to match the application type used to obtain approval of the combination product:
   a. NDA Prior Approval Supplement
   b. BLA Prior Approval Supplement
   c. PMA 180-day Supplement

3. Modified chemical formulation of the device constituent part (not a chemical that would be considered a drug constituent part of the combination product), hardware or software modification of the device constituent part, or other design modification to the device constituent part (without also changing the indication or patient population) for which only new preclinical testing and/or limited confirmatory clinical data are necessary to demonstrate reasonable assurance of safety and effectiveness of the modified device constituent part. For such change, select the submission type to match the application type used to obtain approval for the combination product:
   a. PMA 180-day Supplement
   b. BLA Prior Approval Supplement
   c. NDA Prior Approval Supplement
4. Changes in the biological product constituent part, production process, quality controls, equipment, facilities, or responsible personnel that have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product. Generally, for any such change, select the submission type to match the application type used to obtain approval for the combination product:
   a. BLA Prior Approval Supplement
   b. NDA Prior Approval Supplement
   c. PMA 180-day Supplement
5. Changes in indication or in patient population (without any other change to the combination product itself or to any constituent part except for relevant changes to the labeling) that require substantial clinical data to provide reasonable assurance of safety and effectiveness for the change but either no or very limited new preclinical testing. For such change, select the submission type to match the application type used to obtain approval for the combination product:
   a. PMA Panel-Track
   b. NDA Prior Approval Supplement
   c. BLA Prior Approval Supplement

If the applicable submission requirements for each change do not match (e.g., one change requires a Prior Approval supplement and another requires a Changes Being Effected supplement), then the type of submission should be that associated with the most significant change being submitted. For example, a manufacturer of a drug eluting stent approved under a PMA would like to modify the design of the stent and delete a test for the drug to comply with an official compendium that is consistent with FDA statutory and regulatory requirements. In isolation, the change in the design of the stent would generally require the submission of a PMA 180-day supplement, whereas the change in the test to comply with an official compendium for the drug would generally be submitted in an NDA Changes Being Effected-30 day supplement. In this case, when submitted together, the manufacturer should submit the PMA 180-day supplement for both changes.

1.5 CONCLUSION

Recent breakthroughs in science and technology are transforming the ability to treat diseases and related regulatory challenges for its approval. Different therapeutic delivery solutions give different regulatory challenges to its approval whether it is a single-entity pharmaceutical agent, medical device, cellular therapy, or combinations of any three of these therapeutic solutions. The development of regulatory science and new initiatives in FDA is intended to streamline compliance with CGMP and make effective medication to the patients in a timely manner. The common regulatory goal of all three platforms of therapeutic delivery solutions is to comply with CGMP, although the detailed process of achieving this goal is different.

REFERENCES

1. a. Advancing Regulatory Science for Public Health, October 2010; b. Guidance for Industry: CGMP for Phase 1 Investigational Drugs, July 2008; c. Guidance for Industry: INDs for Phase 2 and Phase 3 Studies. Chemistry, Manufacturing, and Controls Information, May 2003.
2. FDA Recall Notice. Shiatsu recall; August 31, 2011.
3. 21 CFR parts 210 and 211.
4. *FDA Draft Guidance: Classification of Products as Drugs and Devices and Additional Product Classification Issues*, June 2011.
5. 21 CFR parts 600, 601 and 610.
6. *FDA Compliance Program Guidance Manual*.
7. Guidance for Industry: Expedited Programs for Serious Conditions – *Drugs and Biologics*, May 2014.
8. a. Generic Drug User Fee Act; b. Pharm Technol 37(8):24–26.
9. The State of the National Vaccine Plan, 2013 Annual Report, U.S. Department of Health and Human Services.
10. a. Draft Guidance for Industry and Food and Drug Administration Staff: *Expedited Access for Premarket Approval Medical Devices Intended for Unmet Medical Need for Life Threatening or Irreversibly Debilitating Diseases or Conditions*, April 23, 2014; b. Draft Guidance for Industry and Food and Drug Administration Staff – *Balancing Premarket and Postmarket Data Collection for Devices Subject to Premarket Approval*, April 23, 2014; c. FDA Medical Device Innovation Initiative White Paper, CDRH Innovation Initiative, February 2011.
11. Draft Guidance for Industry and Food and Drug Administration Staff: *Applying Human Factors and Usability Engineering to Optimize Medical Device Design*, June 22, 2011.
12. Federal Register, Vol. 78, No. 14, January 22, 2013, 4307.
13. Draft Guidance for Industry and Food and Drug Administration Staff: *Submissions for Postapproval Modifications to a Combination Product Approved Under a BLA, NDA, or PMA*, January 2013.