Medical Device Regulations Lecture-Laboratory Lesson Guide

Student Manual

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APPENDIX B (continued):

I. An Overview of Medical Device Regulations

1. Medical devices

A *device* may be defined as "a piece of equipment or a mechanism designed to serve a special purpose or perform a special function." [Webster's New Collegiate Dictionary]

Medical devices are devices that are intended to promote or maintain health, for example, by aiding in the diagnosis, prevention, or treatment of disease. In contrast to devices, *drugs* are chemical substances and *biologics* are biologically-derived materials used in the diagnosis, prevention, or treatment of disease.

Within the past few years, hybrids that consist of, for example, a device that emits a drug, have been developed.

Examples of medical devices include a broad range of products and underlying technologies, and the risks and benefits to patients also vary widely depending on the type of device. Examples of the range of medical devices include relatively low-technology and non-invasive devices such as stethoscopes, blood pressure cuffs, bandages, and eyeglasses, on the one hand, to sophisticated x-ray and ultrasound diagnostic equipment, and implantable devices such as artificial heart valves, pacemakers, and automatic defibrillators, on the other.

The function of many medical devices depends upon electronic components (discrete and/or integrated circuits) and transducers. These electronic medical devices may employ techniques such as signal processing, feedback control, and pattern recognition, and may include automation relying on analog, software, or firmware programming.

2. Regulation of medical devices

Each country has its own regulations (or relative absence of regulations) relating to the importation, export, manufacture, and sale of medical devices. Because the regulations within the United States are among the most rigorous in the world, US regulations deserve considerable attention. However, since medical device companies often market world-wide, some discussion of regulation outside the US is useful.

2.1. The basis of regulation of medical devices in the US

The US Food and Drug Administration (FDA) regulates the importation, manufacture, and sale of medical devices in the United States based upon the Federal Food, Drug, and Cosmetic Act (FFDCA) and its amendments. The original FFDCA (enacted 1938) did not give FDA authority for the pre-market approval of devices, authority that it was given for drugs; otherwise, devices were regulated as drugs. However, the expansion of medical device technology after World War II, an increase in quack devices, and instances of relatively widespread problems with the safety or effectiveness of some devices (for example, the Dalkon Shield intrauterine device) led to Congressional action. In 1976, an amendment specifically authorizing FDA to closely regulate medical devices, including requiring pre-market approval of high-risk devices, was enacted.

For the US, there is a hierarchy of documents relating to FDA regulations: 1) laws, such as the FFDCA and its amendments, provide a general basis; 2) specific regulations are listed in the Code of Federal Regulations (CFR); and 3) FDA guidances, which provide further details, based on the CFR provisions, on

how to communicate information to FDA generally or the type of information required for specific device types.

Before regulations are finalized in the CFR, they are generally published in proposed form and then subject to a comment period, allowing industry and individuals to suggest changes. The suggested changes and the FDA's rationale for accepting or rejecting changes are published with the final regulations.

The FDA guidances are considered draft documents and in themselves are not necessarily legally binding. Manufacturers generally follow the guidances or provide the FDA with rationales for any deviations.

2.2. The basis of medical device regulations outside the US

Each of the more developed nations has government regulations and a regulatory agency somewhat similar to those of the US and its FDA. For example, Canada has a government regulatory agency called the Health Protection Board that reviews the safety and effectiveness of new medical devices before they may be legally sold in Canada. The countries of the European Union (EU) rely on medical device and quality system standards developed and published by the International Organization for Standardization (ISO). In this EU system, new medical devices are evaluated by a private company, called a *Notified Body*, which the medical device manufacturer selects from among the several EU-approved Notified Bodies. The Notified Body audits documentation (called a *Dossier*) describing the device, it's testing, and the quality system, submitted by the manufacturer. If the documentation is found to be in conformance to the ISO standards for safety and effectiveness, including quality system standards, for the medical device type, the manufacturer receives the CE (abbreviation of *Conformité Européan*) mark for that device. The manufacturer is authorized to display the CE mark on each label of the approved device, and may market it throughout the EU. The US, the European Union, Canada, Japan, and Australia have worked with the ISO to harmonize (make similar or identical) many regulations relating to medical devices. In conformance with a 1997 amendment to the 1976 Medical Device Act, FDA has started a pilot program, similar to the EU review method, in which a manufacturer may send a pre-market notification (510(k)) application for some types of devices for review by an FDA-approved *Third Party Reviewer*.

3. Online information about the FDA, the ISO, and device regulations and standards

The FDA maintains a web site, www.fda.gov, organized by functional Center and Office, with detailed information and a search function. For devices, CDRH maintains full-text PDF versions of guidances and other information, including a device advice section, at www.fda.gov/cdrh. The Code of Federal Regulations is available from the US Government Printing Office and may be available at larger libraries, and recent volumes are available at www.access.gpo.gov/nara/cfr. The ISO web site is www.iso.org; however, a fee is required to view most information at this site.

4. FDA organization

The FDA is organized into several centers and offices based upon administrative function. New medical devices are reviewed for safety and effectiveness within the Center for Devices and Radiological Health (CDRH) by the Office of Device Evaluation, while new drugs are reviewed within the Center for Drug Evaluation and Research (CDER) and new biologics (for example, vaccines) are reviewed within the Center for Biologics Evaluation and Research (CBER). New or modified devices associated with blood collection or processing or with cellular therapies are reviewed in CBER, because of the expertise of that center, but in accordance with medical device laws and regulations. New hybrids (drug-devices or

biologics-devices) may be reviewed by two centers. The FDA's Office of Regulatory Affairs inspects the manufacturing facility for a device when it is approved by the FDA for release to market.

5. FDA enforcement of medical device regulations

When FDA believes there is a problem with a regulated device, law and regulations allow it to take one or more actions, including:

1) Sending the firm manufacturing (or distributing) the device a warning letter.
2) Encouraging the firm to voluntarily recall the device (withdraw it from the market).
3) Requesting or ordering the firm to recall the device; an order may include, if the firm does not comply, seizure of the firm's device stock by federal marshals.
4) Bringing court actions against the firm and the individuals responsible for the firm's alleged violation of regulation and law; such actions can lead to fines levied against a firm and responsible individuals, and convicted persons may also be subject to imprisonment.

FDA classifies each recall into one of three categories:

1) Class I - there is reasonable probability that use of or exposure to a violative product will cause serious adverse health consequences or death.
2) Class II - the use of or exposure to a violative product may cause temporary or medically reversible adverse health consequences or the probability of serious adverse health consequences is remote.
3) Class III - the use of or exposure to a violative product is not likely to cause adverse health consequences.

A *medical device safety alert* is issued in situations where a medical device may present an unreasonable risk of substantial harm; these situations may also be considered recalls.

Note that recall class number is in *descending* order of serious adverse health consequence; in contrast, device classes (Section I.7 of this guide) are in *ascending* order of risk.

As an example of a recall, FDA cites (at www.fda.gov/cdrh/recalls/recall-082404b) a Class I recall by the manufacturer of a software application card used to control the administration of medication for two models of the manufacturer's implantable infusion pumps. The recall was motivated by reports to the manufacturer that in the time duration setting of the infusion software, *hours* were entered into the *minutes* field, resulting in deaths and injuries due to drug overdose.

As an example of an enforcement action, FDA cites (at www.fda.gov/oc/whitepapers/enforce) that a large medical device company was fined $92.4 million for failing to report malfunctions of a medical device to the FDA.

6. General Controls are required by FDA for all medical devices

FDA and other regulators evaluate a medical device as a *unit available for sale to the end user* (for example, a physician) for safety and effectiveness; FDA often calls this unit the *finished medical device*. Thus, usually the medical device system, including its packaging, labeling, and sterilization (if any) are evaluated, while components of the device, such as circuit elements and transducers and software, are not regulated individually, but in relation to the device as a whole. However, if the medical device unit

available for sale *to the end user* is a replacement part or component, such as an electrode, transducer, or a software update, that medical device is regulated.

General Controls include:

1) Establishment Registration with FDA of each company that is required to register under 21 CFR Part 807.20; such companies include manufacturers, distributors, repackagers, and relabelers.
2) Medical Device Listing with FDA of each device type to be marketed.
3) Manufacture of devices in accordance with Good Manufacturing Practice (GMP) in accordance with 21 CFR Part 820.
4) Labeling of devices in accordance with labeling regulations in 21 CFR Part 801 or 809.
5) Submission of a pre-market notification [510(k)] to FDA prior to marketing a device.

GMP and pre-market notification are explained below.

7. FDA classification of devices

FDA assigns each device or type of device into one of three classes:

1) Class I - subject to General Controls
2) Class II - subject to Special Controls (including General Controls)
3) Class III - subject to Premarket Approval (including General Controls)

This classification method is used because devices of different types present very different levels of complexity of design, underlying technology, and risk to the patient. Note that device class number is in *ascending* order of risk to the patient in case of a device problem; in contrast, recall class number (Section I.5 of this guide) is in *descending* order of serious adverse health consequence;

Class I devices are subject to the least regulatory control. Most Class I devices are exempt from the premarket notification and/or good manufacturing practices regulation. They present minimal potential for harm to the patient (or to the medical professional user) and are often simpler in design than Class II or Class III devices. Examples of Class I devices include elastic bandages, examination gloves, and hand-held surgical instruments.

Class II devices are those for which general controls alone are insufficient to assure safety and effectiveness, and existing methods are available to provide such assurances. In addition to complying with general controls, Class II devices are subject to special controls. Special controls may include special labeling requirements, mandatory performance standards, and post-market surveillance. Examples of Class II devices include powered wheelchairs, infusion pumps, and surgical drapes. Most Class II devices are subject to *premarket notification* (510(k)).

Class III devices are subject to the most stringent regulatory controls. Class III devices are those for which insufficient information exists to assure safety and effectiveness solely through general or special controls. Class III devices are usually those that support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury.

Class III devices are subject to premarket approval, a required process of scientific review to ensure their safety and effectiveness. Not all Class III devices require an approved premarket approval application to be marketed. Class III devices that are equivalent to devices legally marketed before May 28, 1976 (*preamendment* devices) may be marketed through the premarket notification [510(k)] process until FDA has published a requirement for manufacturers of that type of device to submit premarket approval data.

Class III devices that require an approved premarket approval (PMA) application to be marketed are those:

1) regulated as new drugs prior to May 28, 1976, also called transitional devices.
2) devices found not substantially equivalent to devices marketed prior to May 28, 1976.
3) Class III preamendment devices which, by regulation in 21 CFR, require a PMA.

Examples of Class III devices that require a PMA include replacement heart valves, silicone gel-filled breast implants, and implanted cerebella stimulators.

Class III device that can be marketed with a premarket notification [510(k)] are those *postamendment* (that is, introduced to the US market before May 28, 1976) Class III devices that are *substantially equivalent* to *preamendment* Class III devices and for which the regulation calling for the PMA has not been published in 21 CFR.

An example of a Class III device type that currently requires only a premarket notification [510(k)] is a new implantable pacemaker.

Device product classifications for device types are listed in the FDA's online searchable Product Classification Database, www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/classification.cfm, with some links to the CFR where further information may be located.

8. Premarket Notification (510(k))

Each person or company (*applicant*) seeking to sell a new or modified device that is in Class I, Class II, or, in some cases, Class III, in the US must submit a *premarket notification (510(k))* to FDA at least 90 days before the device is marketed, unless the device is exempt from 510(k) requirements (21 CFR 807). Devices that are exempt from 510(k) are listed by FDA; they are low-risk devices such as, for example, stethoscopes, heart valve sizers, and pacemaker current leakage testers.

A 510(k) is a premarketing submission to FDA to demonstrate that the device to be marketed is as safe and effective as (and thus *substantially equivalent* to) a legally marketed device that is not subject to premarket approval. The applicant must compare its 510(k) device to one or more similar devices currently and legally on the US market (called a *predicate device*) and make and support claims of substantial equivalency. A legally marketed device is one that was legally marketed prior to May 28, 1976, or a device that was reclassified from Class III to Class II or Class I, or a device that has been found substantially equivalent to such a reclassified device through the 510(k) process, or one established through Evaluation of Automatic Class III Definition (FDA reclassification of certain Class III devices to Class II or I).

A 510(k) is required for a device if: 1) the device is being introduced into commercial distribution (marketing) in the US for the first time; 2) there is a change or modification to a device that is already

marketed, if the change or modification could significantly affect device safety or effectiveness; 3) a change is proposed in the intended use of a device already in commercial distribution. When a change or modification to a currently marketed device is to be made, it is the responsibility of the person or company marketing the device to decide whether the change or modification significantly affects safety and effectiveness. Changes in intended use are usually indicated by changes in claims for a device in its labeling or advertising. If the company believes the modification does not significantly affect safety or effectiveness and documents its evaluation process under design control, it need not submit a 510(k) but notifies the FDA of the change in its yearly report; however, FDA may take action against the company (for example, forcing a product recall) if it finds that the change did require a 510(k).

A device is substantially equivalent to a predicate device if, in comparison to the predicate device, it: 1) has the same intended use **and** 2) has the same technological characteristics **or** 3) has different technological characteristics *that do not raise new questions of safety and effectiveness* and the applicant *demonstrates that the device is as safe and effective* as the predicate device. A claim of substantial equivalence does not mean that the new and predicate devices are identical. Substantial equivalence is established with respect to intended use, design, energy used or delivered, materials, performance, safety, effectiveness, labeling, biocompatibility, standards, and other applicable characteristics.

The FDA, based upon the information submitted by the applicant, determines whether or not the device is substantially equivalent, usually within 90 days of the submission. Until the applicant receives an FDA order declaring a device substantially equivalent, it may not proceed to market the device. Once the device is determined to be substantially equivalent, it can then be marketed in the US. If FDA determines that the device is not substantially equivalent, the applicant may: 1) resubmit another 510(k) with new data; 2) file a petition for reclassification; or 3) submit a premarket approval application (PMA).

The persons or companies that must submit a 510(k) include: 1) domestic manufacturers of finished medical devices who intend to sell the devices in the US market; 2) specification developers of finished medical devices who intend to sell the devices in the US market, even if the devices are manufactured by another person or company; 3) repackagers or relabelers who make labeling changes, or whose operations significantly affect the device; and 4) foreign manufacturers or exporters, or their US representatives, of finished medical devices who intend to sell the devices in the US market.

To streamline the evaluation process for premarket notification, FDA has developed the *New 510(k) Paradigm*, which in some instances presents medical device manufacturers with two new and somewhat simpler and potentially faster optional approaches for obtaining marketing clearance for devices subject to 510(k) requirements. The New Paradigm maintains the *Traditional* 510(k) method for demonstrating substantial equivalence, but adds:

1) the *Special* 510(k) method that may be used for only for a modification of a device that has been previously cleared for market by the 510(k) process, and a) the modification does not change the intended use, b) the modification does not have the potential of changing the fundamental technology of the device (such as implementing automation into a previously manual device), and c) the modification is done under Design Controls within a Quality System; and
2) the *Abbreviated* 510(k) method for only a device for which the manufacturer has relied on a) a guidance document, b) a special control, or c) an FDA-recognized standard to establish substantial equivalence.

More information about premarket notification can be found at: www.fda.gov/cdrh/devadvice/314, www.fda.gov/crdh/devadvice/3143 (Traditional 510(k)), www.fda.gov/crdh/devadvice/3144 (Special 510(k)), www.fda.gov/crdh/devadvice/3145 (Abbreviated 510(k)), and www.fda.gov/crdh/k863 (Guidance on the Premarket Notification Review Program, dated 6/30/1986), and at the URLs referenced at those sites.

9. Premarket Approval (PMA)

Premarket Approval (PMA) is the FDA process of scientific and regulatory review to evaluate the safety and effectiveness of Class III medical devices (21 CFR 814). Due to the level of risk associated with Class III devices, FDA has determined that general and special controls alone are insufficient to assure the safety and effectiveness of Class III devices. Therefore, these devices require a premarket approval application to obtain marketing clearance.

Some Class III preamendment devices (legally marketed in the US before May 28, 1976) may require a Class III 510(k); FDA may call for PMA approvals for such transitional devices by a notice published in the CFR.

PMA is the most stringent type of device marketing application required by FDA. The applicant must receive FDA approval of its PMA application prior to marketing the Class III device. PMA approval is based on a determination by FDA that the PMA contains sufficient valid scientific evidence to assure that the device is safe and effective for its intended use(s). A Class III device that fails to meet PMA requirements is considered to be adulterated under section 501(f) of the Federal Food, Drug, and Cosmetic Act and cannot be legally marketed.

An approved PMA is, in effect, a private license granting the applicant (the PMA owner) permission to market the device. The PMA owner, however, can authorize use of its data by another.

FDA regulations provide 180 days to review the PMA and make the determination of safety and effectiveness for the intended use(s). However, actual review times are generally longer than 180 days. Before approving or denying a PMA, the appropriate FDA advisory committee may review the PMA at a public meeting and provide the FDA with the committee's recommendation on whether FDA should approve the submission. After FDA notifies the applicant that the PMA has been approved or denied, a notice is published on the Internet 1) announcing the data on which the decision is based and 2) providing interested persons an opportunity to petition FDA within 30 days for reconsideration of the decision.

FDA approval of a *PMA supplement* is required to legally market a changed or modified Class III device that has received a PMA approval.

It is not unusual for FDA to respond to a PMA or PMA supplement application with a "Not Approvable" letter to the applicant, listing questions or issues to be resolved. In response, or in the case that some significant new information becomes available, an applicant may submit a *PMA amendment* to FDA containing information to modify a pending PMA application or PMA supplement application.

FDA requires that a PMA application contain administrative and technical content. If FDA finds errors or lack of completeness, compared to the published checklist, in the administrative section, it will refuse to file the PMA application and will not proceed with the review of the technical content.

The technical content usually provides the results of 1) non-clinical laboratory studies and 2) clinical investigations. The non-clinical laboratory studies may include engineering analyses, and microbiology, toxicology, immunology, biocompatibility, stress, wear, shelf life, and other laboratory or animal tests. Non-clinical studies for safety evaluation must be conducted in compliance with 21 CFR 58 (Good Laboratory Practice for Non-clinical Laboratory Studies).

Clinical investigations for a device before approval of its PMA are conducted under an Investigational Device Exemption (IDE). The clinical investigation section includes study protocols, safety and effectiveness data, adverse reactions and complications, device failures and replacements, patient information, patient complaints, tabulations of data from all individual subjects, results of statistical analyses, and any other information from the clinical investigations.

Numerous device-specific FDA guidance documents that describe PMA application data requirements are available. A database listing the guidance documents is available on the Internet at www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfGGP/Search.cfm.

10. Clinical studies of a new or modified device (IDE)

An *investigational device exemption* (IDE) allows an investigational device to be used in a clinical study intended to collect safety and effectiveness data required to support a PMA or Premarket Notification (510(k)) submission to FDA. Most 510(k) applications do not require clinical studies. An "investigational device" is a device that is the object of clinical (human subject) study for to determine its safety and/or effectiveness and is a device: 1) that has not been cleared for marketing; 2) that includes modification of a device cleared for marketing; or 3) cleared for marketing that has a new intended use.

An approved IDE permits a device to be shipped lawfully for the purpose of conducting investigations of the device without complying with other requirements of the Federal Food Drug and Cosmetic Act that would apply to devices in commercial distribution. The sponsor of the investigation (the initiator of an investigation; typically, the manufacturer or distributor) is not required to submit a PMA or 510(k), register their establishment, or list the device while the device is under investigation. The sponsors of an IDE is also exempt from the Quality System regulations (21 CFR 820; Sections I.10 - I.12 in this guide) except for the requirements for Design Controls (21 CFR 820, Subpart C; Sections I.13 - I.16 and Section II in this guide).

A *significant risk device* is an investigational device that: 1) is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a (human) subject; 2) is for use in supporting or sustaining human life and represents a potential for serious risk to the health, safety, or welfare of a subject; 3) is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or 4) otherwise presents a potential for serious risk to a subject.

Clinical evaluation or study of an investigational device requires:
1) An IDE (21 CFR 812) approved by an Institutional Review Board (IRB; a hospital committee authorized to approve clinical research (21 CFR 56))
2) If the study involves a significant risk device, the IDE must also be approved by the FDA (21 CFR 812)
3) Informed consent from all patients (21 CFR 50)

4) Labeling for investigational use only (21 CFR 812)
5) Monitoring of the study (21 CFR 812)
6) Required records and reports (21 CFR 812)

Good Clinical Practices (GCP) refers to the regulations and requirements that must be complied with during a clinical study. These regulations apply to the manufacturers, sponsors, clinical investigators, institutional review boards, and the medical device. The primary regulations are: 1) Investigational Device Exemptions (21 CFR 812); 2) Protection of Human Subjects (21 CFR 50); 3) Institutional Review Boards (21 CFR 56); Financial Disclosure by Clinical Investigators (21CFR 54); and Design Controls of the Quality System Regulation (21 CFR 820 Subpart C).

Investigations that are exempt from IDE approval (but may not be exempt IRB review and informed consent regulations) are described in 21 CFR 812.2(c); such studies include:
1) a legally marketed device when used in accordance with its labeling;
2) a diagnostic device if it complies with the labeling requirements in 21 CFR 809.10(c) and if the testing: a) is non-invasive; b) does not require an invasive sampling procedure that presents significant risk; c) does not by intention or design introduce energy into a subject; and d) is not used as a diagnostic procedure without confirmation by another medically established diagnostic product or procedure;
3) consumer preference testing, testing of a modification, or testing of a combination of devices if the devices are legally marketed devices and it the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk;
4) a device intended solely for veterinary use;
5) a device shipped solely for research with laboratory animals and contains the labeling "Caution - Device for investigational use in laboratory animals or other tests that do not involve human subjects."

Details on Investigational Device Exemptions are available at www.fda.gov/cdrh/devadvice/ide.

11. Good Manufacturing Practice (GMP)

Good Manufacturing Practice (GMP; also called *Current Good Manufacturing Practice* (CGMP)) are a set of requirements established by FDA (listed in 21 CFR 820; supplemental information in 21 CFR Parts 808 and 812) and by ISO (ISO 9001 and ISO DIS 13485) to assure that medical devices are produced to appropriate standards and with appropriate documentation. Within the past decade or so, FDA and ISO have come to view GMP as only one part of a broader set of concepts and regulations called a *Quality System.*

12. Quality System (QS)

A Quality System (QS) is a set of documented practices and the documents themselves, which includes practices and documentation appropriate for the specific medical device(s) designed or manufactured by a manufacturer, in accordance with US FDA regulation (21 CFR 820.5 and 21 CFR 820.20), and consistent with International Organization for Standardization standards (ISO 9001 and ISO DIS 13485). FDA believes that an adequate and properly implemented quality system, an approach that goes far beyond superficial quality-control inspection, has a high likelihood of preventing the design, manufacture, and shipment of defective products.

The elements of a quality system include the following:

1) Management (Company Executive) Responsibility (21 CFR 820.20)

2) Formal, Documented QS (21 CFR 820.5, 820.20, 820.180, 820.181, 820.186)
3) Document Controls (21 CFR 820.40)
4) Employee Training (21 CFR 820.25)
5) Design Controls (21 CFR 820.30)
6) Component Selection
    a) Purchasing Controls (21 CFR 820.50)
    b) Receiving Acceptance (21 CFR 820.80(b))
7) Labeling Content (21 CFR 820.120)
8) Process Quality (21 CFR 820.60, 820.70, 820.72, 820.75, 820.80, 820.86)
9) Approval of Product
    a) Acceptance of In-Process and Finished Product (21 CFR 820.80)
    b) Control of Non-Conforming Product (21 CFR 820.90)
10) Quality Acceptance Activities (21 CFR 820.80, 820.181, 820.20, 820.100)
11) Quality System Audits (21 CFR 820.22)
12) Quality System Maintenance (21 CFR 820.20)
13) Complaint Files, Investigations, and Corrective Actions (21 CFR 820.198, 820.100)
14) Medical Device (Adverse Field Event) Reporting (21 CFR 803)
15) Servicing (if applicable) (21 CFR 820.200)
16) Statistical Methods (21 CFR 820.250)

This guide will provide additional details on Document Controls and Design Controls. The details of the other quality system elements are beyond the scope of this guide. Additional information on Quality Systems is available from FDA (www.fda.gov/cdrh/qsr).

13. Document Controls

Document Controls are the written procedures that are required to be used by a manufacturer to maintain current revision valid documents (including the Quality System Manual, device specifications and engineering drawings, manufacturing procedures, and indeed all documents required by 21 CFR 820). Document Controls requirements include:

1) Approval of documents by an authorized individual, with a documented, dated signature, before they can be issued or become effective.
2) Approval of changes in documents by an authorized individual with the same function as the original reviewer and approver, with a documented, dated signature, before they can be issued or become effective.
3) Records of changes to documents shall be maintained and shall include a description of the change, identification of the affected documents, the signature of the approving individual(s), the approval date, and the effective date.
4) Current valid documents shall be available at all locations where they are used or needed.
5) Obsolete documents shall be promptly removed from all points of use or otherwise prevented from unintended use.

14. Design Controls

Design Controls are documented practices that are required by the FDA (21 CFR 820.30) of all manufacturers, including specification developers, of Class II and Class III and a selected group of Class I

devices, during the development of such medical devices. The failure of any of such devices would be likely to adversely affect patient health or safety.

The FDA considers design control requirements to be the basic controls needed to ensure that a device being designed performs as intended when produced for commercial distribution. Design controls need not be applied to research efforts; however, the manufacturer must explain to FDA where in its design and development process the design becomes subject to design controls.

The Class I devices subject to design controls include the following:

1) Any device automated with computer software
2) Catheter, Tracheobronchial Suction
3) Glove, Surgeon's
4) Restraint, Protective
5) System, Applicator, Radionuclide, Manual
6) Source, Radionuclide Therapy

15. Benefits of Design Controls

FDA considers that implementation of Design Controls by manufacturers should:

1) Increase the safety of patients, who are the ultimate users of biomedical devices, by requiring device manufacturers to carefully document, verify, validate, and review device designs during development, before release to market.
2) Increase the over-all efficiency of the design process, by:
    a) providing a rational and documented path for the design process;
    b) reducing the risk of redesign after a device is released to market.

16. Elements of Design Controls

The manufacturer or specification developer of a medical device that is required by FDA regulations to be developed under Design Controls (Section 10 above) is obligated to implement the elements of Design Controls, including:

1) Establish and maintain documented procedures for Design Control (21 CFR 820.30(a); references below are all from 21 CFR Part 820.30).
2) Establish and maintain plans that describe design activities, including how input is provided to the development process, and define responsibility for implementation (820.30(b)).
3) Identify the design input or requirements for the device (820.30(c)).
4) Develop the design output or specifications for the device (820.30(d)).
5) Hold design reviews at appropriate points during the design process to identify and solve problems with the design or the design process (820.30(e)).
6) Verify that the design output meets the design input (820.30(f)).
7) Validate that the design meets defined user needs and intended uses (820.30(g))
8) Validate any software used in the device (820.30(g)).
9) Transfer the device design to production specifications (820.30(h)).
10) Control of changes (through document control and by verification and/or validation) to the design during the design process and changes in the design of products on the market (820.30(i)).
11) Document design control activities in the design history file (820.30(j)).

17. Major features of Design Controls

1) Design Controls are required once a design and development project begins; they do not apply to a conceptual or research effort, although such efforts may precede a development project.
2) Implementation and maintenance, including employee training, of Design Controls are the responsibility of the executive management of a biomedical device manufacturer.
3) Design Controls provide a feedback process with potentially iterative steps, with scheduled and documented Design Reviews serving as decision points.
4) Design Reviews provide the opportunity to systematically evaluate the design to objectively judge whether to proceed with or revise the design (a feedback process).
5) Design Controls require recording the history of the development of a device in a Design History File (DHF):
   a) The DHF provides a record for the manufacturer's future use.
   b) FDA may audit the DHF to evaluate the manufacturer's conformance to Design Controls.

II. Design and Development with Design Controls - The Process

Many technically trained individuals in the medical device industry will require a thorough understanding of Design Controls. Therefore, this section of the guide provides a detailed outline of the design and development process employing Design Controls. The manufacturer's Quality System Manual is required to include a generic project plan with steps identical or equivalent to steps 1 through 16 below to control the design and development process. In a manufacturer's generic project plan, department responsibilities and approvals for transitions between steps would be identified; these are not shown here because they are specific to each manufacturer.

1. Design and Development Project Starts
   a. Generally preceded by a Conceptual or Research Phase
   b. Executive management initiates the Project; Project Leader and Team and initial resources are assigned by management
2. A *Design Input* document is prepared by the Project Leader and Team:
   a. Under document control
   b. Quantitatively details the requirements for a proposed device
   c. Based upon customer input, marketing and engineering information
   d. Design Review of the Design Input is conducted; Project Team and management decide to proceed or to revise the Design Input
3. A *Project Plan document* is prepared by the Project Leader and Team
   a. Under document control
   b. Consistent with a generic development project plan outlined in the Quality System
   c. Specifies what is to be done when and by whom
   d. Identifies and schedules decision points such as Design Reviews
   e. Will be revised as circumstances dictate
4. *The first Design* Output documents, consisting typically of *Specifications and Engineering Drawings*, are prepared
   a. Under document control
   b. Represent a response to the Design Input
   c. If the device is to be supplied sterile, sterile packaging must be included in the Design Output
5. *Device Prototypes* are built conforming to the Design Output
   a. May include bread-board units for Verification (Sections 7 & 8)
   b. Must include production-grade units for Validation (Sections 9 & 10)

6. A *Risk Analysis* such as Failure Modes and Effects Analysis (FMEA) is conducted
   a. Evaluation of the reliability, quality, or safety implications of a design
   b. Under document control; required in DHF
   c. For significant design changes during Project, the Risk Analysis is updated; the final Risk Analysis is performed on the final Design Output.
7. *Verification Protocols* describe how Verification Tests and Analyses are to be performed
   a. Under document control
8. *Verification Tests and Analyses* are conducted on the Design Output (Device Prototypes)
   a. Verification is the confirmation by examination and provision of objective evidence that specified requirements have been fulfilled
      i. Verification is intended to check whether or not the Design Output satisfies the requirements called out in the Design Input
   b. Usually, a relatively small number of device units (and subunits) are tested in a verification
   c. Analysis by computer modeling (for example, finite element analysis) may be conducted as appropriate for the device
   d. Results of Verification Tests and Analyses are recorded in written Reports that are retained in the DHF
   e. Any deviations or exceptions to the Protocol are recorded in the Report
   f. A Design Review is conducted to evaluate the Verification Tests and Analyses; the decision is made by the Project Team and management to proceed or to revise the Project Plan (Section 3)
9. *Validation Protocols* describe how Validation Tests and Evaluations are to be performed
   a. Under document control
10. *Validation* Tests and Evaluations are conducted on the Design Output (Device Prototypes)
   a. Validation is the confirmation by examination and provision of objective evidence that the particular requirements for a specific intended use can be consistently fulfilled
   b. To assure that requirements are consistently fulfilled, additional device prototypes, fabricated to cover the ranges of specification tolerances, or to provide a statistically valid sampling, may be required for validation testing
   c. Validation may include evaluations by device users (health care professionals) but with no use on patients
   d. Results of Validation Tests and Evaluations are recorded in written Reports that are retained in the DHF
   e. Any deviations or exceptions to the Protocol are recorded in the Report
   f. A Design Review is conducted to evaluate the Validation Tests and Evaluations; the decision is made by the Project Team and management to proceed or to revise the Project Plan (Section 3)
11. Final *Labeling and Packaging* are specified
12. Final Design Output (the device and its specifications, drawings, labeling, and packaging as recorded the DHF) is considered ready for *Transfer to Manufacturing*
13. To *Transfer the design* to Manufacturing, processes are developed and documented (under document control) to reliably fabricate the device, conforming to Design Output specifications, under production conditions
   a. Realistic manufacturing tolerances and their effects on product fit, form, and function should be considered (including by Risk Analysis - FMEA) as early as possible in the Design and Development Project to assure an efficient Transfer to Manufacturing and consistent product quality
14. Manufacturing *Process Validation* is conducted to establish by objective evidence that each

process *consistently* produces a result or product meeting its predetermined specification
   a. A Process Validation is required when the result of the process cannot be fully verified by subsequent inspection and testing
   b. To assure that the process consistently produces results meeting the predetermined specifications, statistical reasoning may be used (for example, by testing a number of samples from a number of manufacturing lots)
   c. A sufficient number of units and lots must be produced by the manufacturing process for all Process Validations
   d. If the device is to be supplied sterile, sterilization validation of the device in its sterile packaging is required
   e. Process Validation Reports are retained in the DHF
   f. A Design Review is conducted to evaluate the final Design Output and the Transfer to Manufacturing, including any Process Validations performed; the decision is made by the Project Team and management to proceed or to revise the Project Plan (Section 3)

15. A *Clinical Study*, evaluating the device in a limited number of patients under conditions specified in written Clinical Protocols, may be required by FDA or non-US regulatory agencies to provide a high degree of assurance of device safety and effectiveness
16. *Submissions* are forwarded to the FDA and to non-US regulatory agencies; for FDA, the submission may be one of the following:
   a. Request to be allowed to market the device in the US, based on the devices substantial equivalence to a currently US-marketed approved device (510(k) procedure; see Section I.8)
   b. Request to be allowed to conduct a Clinical Study (IDE, see Section I.10)
   c. Request to be allowed to market the device in the US, based on a substantial body of evidence establishing with a high degree of assurance the safety and effectiveness of a device (Pre-Market Approval(PMA) Application, see Section I.9)
17. Following the submission of a Premarket Notification (510(k)), FDA action may be either to find the device
   a. Substantially equivalent to a predicate device (allowing marketing) or
   b. Not substantially equivalent (not allowing marketing) - applicant may then
      i. Submit new 510(k) with new information
      ii. File a PMA application
      iii. Petition FDA for reclassification
18. Following the submission of a request for an IDE, FDA action may be either Approval or Non-Approval (the latter usually accompanied by questions or requirements for changes).
19. Following the submission of a PMA application, FDA action may be:
   a. Approval (the device may be marketed) or
   b. Conditional Approval (the device may be marketed only after the manufacturer fulfills certain conditions, such as agreeing to special post-market surveillance)
   c. Non-Approval (usually, the FDA raises questions that the manufacturer must address; such questions may in some cases require additional tests or even redesign, followed by submission of a PMA amendment)

III. Supplementary Information on Design Controls

1. Design and Development Project Starts
   a. Executive management typically decides to begin (or not begin) a project based on a variety of business, manufacturing, and technical considerations; the reasons are generally beyond the scope of regulatory requirements. However, for completeness, here is a list of items management may consider to justify starting or not starting a project:

i. Is there a market for the new (or modified) device?
ii. How large is the market, does it fit the business' expectation?
iii. Is the market likely to grow?
iv. What is the competition?
v. Does the company have the technical capability to design & develop the device? What are the estimated times and costs?
vi. Does the company have the manufacturing capability to follow development with products, or would new/outside resources be required? What are the estimated times and costs?
vii. What is the regulatory path for the device (premarket notification or premarket approval)? What are the estimated times and costs?
viii. Would clinical investigations be required? What are the estimated times and costs?

2. Project Team Membership
   a. Generally includes at least one representative from each functional department that has a role in product development, and is thus dependent on the manufacturer's organization.
   b. Project team membership by functional department is defined in a manufacturer's Quality System Manual section on Design Controls.
   c. For a typical manufacturer, functional departments represented on a project team may include, for example, Product Development (R&D Engineering), Marketing, Quality, Manufacturing, and Regulatory Affairs. Depending on the manufacturer's procedures, specialists in areas such as document control (technical or engineering services), packaging, microbiology/sterilization, and testing methodologies may be either project team members or consultants to the project team.
3. Project Plan Document
   a. The simplest project plan format is a listing of tasks, their respective start and end dates, and the group or individual responsible for each task.
   b. More sophisticated project plan formats are Gantt and PERT (or CPM) charts.
      i. Gantt charts may show dependencies and a graphic display of task duration.
      ii. PERT (or CPM) charts show dependencies and the critical path
4. Risk Analysis by Failure Modes and Effects Analysis (FMEA)
   a. FMEA is a method intended to systematically identify each apparent potential manner of failure (failure mode) in a device and the likely effect of each such failure on other components, the device as a whole, and the safety and effectiveness of the device.
   b. Each identified failure mode is characterized with a Risk Priority Rank Number (RPRN or RPN) to assign priorities to concerns that may require quality action or design improvement.
   c. The RPN is defined as the product of three estimates, each based on engineering knowledge or judgment:
      i. The severity of the effect of a particular failure mode;
      ii. The probability of that particular failure mode occurring;
      iii. The likelihood that the cause of the failure mode or incipient failure would be detected prior to use or distribution.
      iv. A scale for the estimates of severity of effect, probability of failure occurring, and likelihood of detection must be adopted before the FMEA is conducted. Typically, the scales are standardized in the company's QS Design Control procedures so that a high or low RPN indicates a high or low priority, respectively, for corrective quality action. The potential failures rated with the highest RPNs are subjected to corrective quality action first; when these failures are addressed to produce significantly lower RPNs, failures with the next highest RPNs are addressed. Here is an example of FMEA scales:

(a) Severity of effect: 1, none; 2, minor (small cost, no harm to patient); 3, intermediate (significant cost, inconvenience to patient); 4, high (non-life threatening risk to patient's health or potential for minor injury); 5, extreme (risk to patient's life)
(b) Probability of failure: 1, low; 2, intermediate; 3, high
(c) Likelihood of detection: 1, high; 2, intermediate; 3, low
(d) Calculated RPN: 1 (lowest) to 45 (highest)

5. Labeling and Packaging
   a. Labeling includes, but is not limited to: a description of the device (its type), its sterile (or non-sterile) condition as supplied to the user, its size, the manufacturer's (or distributor's) name, address, and telephone number, lot and/or serial number, expiration date (use-by date for a sterile device), and instructions for use.
   b. Packaging includes, for example:
      i. The container for the unit, which, if supplied sterile, is often a double pack - the outer pack is intended to be opened by a non-sterile scrub nurse in an operating room, and the inner pack is intended to be dropped from the outer pack into the sterile field, to be opened under sterile conditions. These containers must be capable of undergoing sterilization without sustaining damage or distortion.
      ii. The shipping container and protective packaging materials, which must be capable of preventing damage to the device during shipping (may be assumed to include dropping of the package, and variations in ambient temperature and air pressure).
6. Transfer to manufacturing
   a. Design planning for manufacturing, including sterilization, must begin early in the design process to reduce the risks of increasing development time and costs for redesign.
   b. Inclusion of a representative from the manufacturer's Manufacturing Department on the project team is common and is intended to assure that manufacturing considerations are taken into account during design and development (Design for Manufacturing).

IV. Suggested Lesson Plan

This Lesson Plan assumes 1) presentation of a large body of information in the first two lessons, to provide the background on Design Controls and Regulatory Submission types required for the remainder of the course; and 2) simulation of parts of the design and development process, using model devices such as those studied in the course, to reinforce the concepts introduced in the first lessons. For each lesson, this Lesson Plan identifies corresponding sections of the *Lesson Guide* (*LG*) and the FDA's *Design Control Guidance for Medical Device Manufacturers* (*DCG*) or other reference.

1. Lesson 1: A Design and Development Project Starts.
   a. Summary
      Knowledge of FDA regulations is an essential prerequisite to successfully pursuing medical device design and development for products to be sold in the US market. With that knowledge and relevant business information, a design and development project may be started, as illustrated in this lesson.
   b. Critical teaching points
      i. Reading assignment - Read before the lesson
         Overview of Medical Device Regulatory Basis:
         Lesson Guide (*LG*): Section I.1 through and including Section I.5
         Overview of FDA Controls and Device Classification:
         LG: Section I.6 through and including Section I.10
         Overview of Quality Control System and Design Controls :

LG: Section I.11 through and including Section I.17
Design and Development with Design Controls - The Process
LG: Section II
Design Control Guidance for Medical Device Manufacturers (*DCG*): Introduction; Section A, General; Section B, Design and Development Planning; Section J, Design History File

ii. A Design and Development Project follows a Project Plan document
LG, Section II provides a model outline *generic* Project Plan that will be followed in the course. A company's generic Project Plan will show the general steps that need to be followed to complete a Design and Development Project; it will also show which departments are responsible for leading or contributing to each required project step. Detailed project planning, which includes identification of specific tasks, the individuals responsible for performing the tasks, and the anticipated start and end dates, requires consideration of the type of device to be developed, its desired requirements, and other factors, and is generally best initiated after the Design Input is clear.
LG: Section II
DCG: Section B, Design and Development Planning

iii. A Design and Development Project has a defined Start
A well-run company has business, manufacturing, regulatory, and technical rationales for starting a Design and Development Project and releasing resources (personnel and funding) for the project.
LG: Section II.1 and Section III.1
DCG: Section A, General

iv. Project Teams
Team members should represent all departments of a company that would be active in the design and development process. There should be at least one representative of each of the following functions: Product Development (R&D) Engineering, Marketing, Quality Systems, Production - Manufacturing, Regulatory Affairs, and Microbiology - Sterilization. One team member, commonly a representative of R&D Engineering, serves as Project Leader.
LG: Section III.2

c. Exercises
   i. Review and Discuss a Generic Project Plan. [LG: Section II]
   ii. Model the Start of a Design and Development Project. [LG: Section III.1]
   iii. Model the assembly of a Project Team for the Design and Development Project. [LG: Section III.2]

d. Examples
   i. A constructed (fictitious but realistic) model of the Start of a Design and Development Project is suggested, as follows.
      (1) An intravascular catheter blood pressure measurement system includes pressure transducers embedded in the catheter, differential amplifiers for signal processing, and a display system
      (2) The Marketing Department of a company that manufactures these systems reports that the users (customers), who are primarily interventional cardiologists, would prefer that the catheter have a smaller diameter. This would potentially expand the market for the device (for example, to smaller individuals and pediatric cases) and make insertion of the catheter less risky for all patients. Marketing believes a system with a smaller catheter that otherwise had the same performance as the present system

could be sold at a significantly higher price.

(3) The Product Development (R&D) Department reports that smaller- sized pressure transducers and differential amplifiers have become available, but must be adapted to placement in a smaller catheter in order to create a new product. The new transducers and amplifiers will cost more than the ones in the present device.

(4) The Manufacturing Department reports that it will need new equipment and procedures to fabricate the new catheter, so there will be significant capital expenditures for the new product. Also, the new device will cost more than the present device.

(5) The Regulatory Affairs Department reports that the new product will most likely require a 510(k) clearance rather than a PMA, since it has a predicate device (that is, one with similar technology for the same use already approved for sale in the US) and is not considered a high-risk device.

(6) Based on the above information, which in a real case generally includes quantitative estimates of market size (unit and dollar volume), capital costs, product costs, and return on investment, the company CEO and Department vice-presidents decide to Start a Design and Development Project for the new, smaller diameter catheter system.

ii. The Instructor or Students may construct similar models of the Start of a Design and Development Project, but for other medical device technologies covered in the course, including, for example:

(1) Blood flow measurement system

(2) ECG measurement system

(3) Cardiac pacemaker

e. Additional references/resources:
Several web sites provide information on product development, but may not discuss regulatory aspects needed for medical devices; examples include www.pdma.org and www.toolkit.cch.com.

2. Lesson 2: Design Input and Design Review Documents.

a. Summary
The Design Input Document and its Design Review are critical to the launch and ultimate success of the Design and Development Project. The Design Input Document translates into quantitative engineering language a comprehensive list of customer needs and other requirements (such as regulatory or industry standards) for the new or modified device. The adequacy of the Design Input is formally evaluated by a documented Design Review, maintained under Document Control including Change Control (changes to the document are only permitted after the dated, signed approval by an authorized individual). During the course of the Project, new information may require revision of the Design Input; such revisions must be documented with a revised Design Input Document and formally evaluated with a documented Design Review.

b. Critical teaching points

i. Reading assignment - read before lesson
LG: Section II.2
DCG: Section C, Design Input (including Assessing Design Input Requirements for Adequacy); Section E, Design Review

ii. A Design Input Document is a quantitative and comprehensive list of customer needs and other requirements. It includes engineering or technical requirements written by Product

Development team members and may be based in part upon qualitative requirements suggested by Marketing team members. The Design Input Document may be revised , under document control, if new information becomes available. A Design Input Document is evaluated for adequacy in a Design Review.

iii. A Design Review Document is the written record of a formal review of a Design and Development Project. Design Reviews are conducted when significant milestones in the Project are reached (for example, completion of each of the following: the Design Input Document, Verification Report, Validation Report, final Design Output Document(s)) and whenever necessary to formally evaluate the status and progress of a Project. In a Design Review, it is a recommended that the reviewers include one or more knowledgeable individuals independent of the Project.

c. Exercises
   i. Produce a section of a model Design Input Document; for purposes of the course simulation, based upon an existing medical device.
   ii. Produce a section of a model Design Review Document for the Design Input section produced for this lesson.

d. Example
   i. Construction of a section of a Design Input Document for an intravascular pressure measurement catheter, using a blend of publicly available and fictitious but plausible information, is illustrated here.
      (1) Purpose: Clinical measurement of the blood pressures in the heart chambers on either side of a heart valve
      (2) Catheter length:
      (3) Qualitative: Can reach heart from the femoral cut-down in adults
      (4) Quantitative: 120 ± 1 cm
      (5) Catheter diameter:
      Qualitative: Able to pass through blood vessels
      Quantitative: 5 french (5/3 mm)
      (6) Transducer type; quantity: miniature strain gage; 2
      (7) Transducer positions: 1) at tip and 2) 5 ± 0.1 cm from tip
      (8) Operating range: -250 to +250 mm Hg
      (9) Overpressure tolerated without damage: -1000 to +1000 mm Hg
      (10) Transducer frequency response:
      Qualitative: High fidelity, accurate reproduction
      Quantitative: Amplitude within 0.1% of peak, 0 to 10 kHz
      (11) Drift:
      Qualitative: Accurate without recalibration for long procedures
      Quantitative: <0.1% for 24 h at 37oC for operating range
      (12) Hysteresis:
      Qualitative: Follows cardiac pressure cycles without recalibration
      Quantitative: <0.1% at 0.1 to 10 Hz at 37oC for operating range
      (13) Sterilization: Can be steam sterilized in autoclave
   ii. The Instructor and Students may construct a model section of a Design Input Document for one of the other technologies covered in the course.

e. Additional references/resources:
   Information on intravascular pressure measurement catheters is available at www.millarinstruments.com.

3. Lesson 3: Detailed Project Plan.
   a. Summary
      i. Detailed Project Plan
         The detailed Project Plan specifies the project tasks, when they must start and end, who is responsible for each task, and the precedent-successor relationships among the tasks.
   b. Critical teaching points
      i. Reading assignment - read before lesson
         LG: Section II.3 and Section III.3
         DCG: Section B, Design and Development Planning
      ii. The detailed Project Plan specifies the project tasks, when they must start and end, who is responsible for each task, and the precedent-successor relationships among the tasks. The detailed Project Plan identifies specific Project Tasks, including Risk Analysis, Verification, Validation, and other Design and Development Project activities, the individuals responsible for carrying out the activities, and start and end dates for the activities. The precedent-successor relationships between activities also are identified. The detailed Project Plan is a controlled document and must be revised as necessary to reflect progress and/or changes in the Project.
   c. Exercises
      i. Produce a section of a detailed Project Plan document for an ECG signal measuring system, assuming and identifying likely Design Input requirements; for example, identify specific verification and validation tests required, identify whether animal studies or clinical investigations would be required, and suggest a likely regulatory path. For purposes of this course, identification of who performs the tasks and start and end dates may not be relevant and so need not be considered, but precedent-successor relations should be identified.
      ii. The Instructor and Students may choose to produce a section of a detailed Project Plan for any medical device relevant to the course.
   d. Example
      Design and Development of an ECG Measurement System
      (Section of detailed Project Plan; precedents shown in square brackets)
      i. Identify/Design ECG electrodes
         (1) Conductive material of electrode
            (a) Topical conductive gel applied for higher conductivity
         (2) Adhesive material
         (3) Backing material
         (4) Surface area required, thickness [i(1), i(2), i(3)]
         (5) Connection to lead [i(3), ii(1)]
         (6) Sterilization method [i(1), i(2), i(3), i(5)]
         (7) Sterile packaging [i(1), i(2), i(3), i(4), i(5), i(6)]
      ii. Identify/Design ECG leads
         (1) Connection to electrode [i(5)]
         (2) Conductor - material, diameter
         (3) Insulation - material, thickness
         (4) Length
      iii. Identify/Design ECG amplifier/recorder unit
      iv. Verify impedance matching of electrodes and leads [i, ii]
      v. Verify impedance matching of leads and amplifier/recorder [ii, iii]
      vi. Validate sterilization method [i]

vii. Verify that sterile electrode is nontoxic to skin (animal test) [i, vi]
viii. Verify that sterile electrode is hypoallergenic (clinical test) [i, vi, vii]
(1) Decide that device is a "significant risk" device
(2) Identify clinical sites, monitoring personnel
(3) Develop clinical evaluation forms
(4) Receive IRB approvals [viii(1), viii(2), viii(3)]
(5) Apply to FDA for IDE for clinical test [viii(1), viii(2), viii(3), viii(4)]
ix. Class II device; prepare Premarket Notification (510(k)) [i through viii]

e. Additional references/resources
i. LG: Section I.10

4. Lesson 4: Design Output.

a. Summary
i. Design Output includes all of the documents and physical units that are generated in response to the needs and requirements listed in the Design Input.

b. Critical teaching points
i. Reading assignment - read before lesson
LG: Section II.4
DCG: Section D, Design Output
ii. The Design Output includes all the documents and physical units that are generated in response to the needs and requirements listed in the Design Input.
Typically, the first items of Design Output prepared in a Design and Development Project are engineering drawings and specifications, followed by prototypes or models, that define a candidate device that embodies as closely as possible the characteristics and performance called for by the Design Input. As the Project advances, the Design Output typically changes, providing a more exact embodiment of the characteristics and performance called for by the Design Input as more information becomes available. Design Output documents are maintained under Document Control, including Change Control.

c. Exercises
i. Produce a section of the Design Output documents for a plethysmograph blood volume/pressure measurement system, assuming and identifying likely Design Input requirements. The Design Output may include, for example, engineering drawings, circuit diagrams, and/or specifications for the components or the system. Because of course time and scope limitations, the section of the Design Output may be less complete than necessary for the purposes of a medical device manufacturer.
ii. The Instructor and Students may choose to produce a section of the Design Output documents for any medical device relevant to the course.

d. Example
i. Section of the Design Output Specification for a Plethysmograph
(1) The plethysmograph transducer will be a tissue impedance sensor.
(2) The sensor will be formed into a tube, inner diameter 3.50 ± 0.02 cm and length 5.00 ± 0.02 cm.
(3) The sensor will be powered by 4 AAA cells in a battery pack, case exterior dimensions (cm): 5 x 2 x 2.

e. Additional references/resources: None

5. Lesson 5: Risk Analysis.

a. Summary
   i. A Risk Analysis evaluates the reliability, quality, and/or safety implications of a design.
b. Critical teaching points
   ii. Reading assignment - read before lesson
   LG: Section II.6 and Section III.4
   K. Crow, *Failure Modes and Effects Analysis (FMEA)*, www.npd-solutions.com/fmea
   FDA, *Do It By Design: An Introduction to Human Factors in Medical Devices*
   iii. Failure Modes and Effects Analysis (FMEA) is a common method for conducting Risk Analysis.
      (1) FMEA is a method intended to systematically identify each apparent potential manner of failure (failure mode) in a device and the likely effect of each such failure on other components, the device as a whole, and the safety and effectiveness of the device.
      (2) Each identified failure mode is characterized with a Risk Priority Rank Number (RPRN or RPN) to assign priorities to concerns that may require quality action or design improvement.
      (3) The RPN is defined as the product of three estimates, each based on engineering knowledge or judgment:
         (a) The severity of the effect of a particular failure mode;
         (b) The probability of that particular failure mode occurring;
         (c) The likelihood that the cause of the failure mode or incipient failure would be detected prior to use or distribution.
      (4) Scales for the estimates of severity of effect, probability of failure occurring, and likelihood of detection must be adopted before the FMEA is conducted.
   iv. The Risk Analysis is updated or repeated as significant design changes are implemented during the Project; the final Risk Analysis reflects the final Design Output.
c. Exercises
   i. Produce a section of a Risk Analysis document, using Failure Modes and Effects Analysis (FMEA), for the sphygmomanometer (stethoscope, cuff, manometer) blood pressure measurement system and its method of use.
   ii. The Instructor and Students may choose to produce a section of an FMEA document for any medical device relevant to the course, including, for example, an ECG measurement system or a plethysmograph system.
d. Example
   i. FMEA of Sphygmomanometer Blood Pressure Measurement System
      (1) Cuff bulb has a hole, bulb cannot maintain pressure, so blood pressure cannot be obtained and test must be repeated
         (a) Severity = 2 (Scale: 1 to 5)
         (b) Probability = 1 (Scale: 1 to 3)
         (c) Likelihood of detection = 2 (Scale: 3 to 1)
         (d) RPN = 2*1*2 = 4
      (2) Manometer mechanism sticks due to contamination inadvertently introduced at manufacture, measurement may be inaccurate
         (a) Severity = 4
         (b) Probability = 1
         (c) Likelihood of detection = 2
         (d) RPN = 8
      (3) Inexperienced or insufficiently trained user cannot reliably detect the Korotkoff sounds

(a) Severity = 4
(b) Probability = 2
(c) Likelihood of detection = 3
(d) RPN = 24

(4) Examination of the RPNs calculated in this example shows that the failure mode to be assigned the highest priority for corrective action is the case of the inexperienced or insufficiently trained user.

e. Additional references/resources: None

6. Lesson 6: *Verification Protocols, Verification Tests, and Reports.*

a. Summary

i. A Verification Test or Analysis is performed as directed by a Verification Protocol, and is intended to check whether or not the performance and characteristics of the Design Output satisfies the Design Input requirements.

b. Critical teaching points

i. Reading assignment - read before lesson
LG: Section II.7 and II.8
DCG: Section F, Design Verification

ii. A Verification Protocol defines how a Verification Test or Analysis is to be performed.

iii. A Verification Test or Analysis is intended to check whether or not the performance and characteristics of the Design Output (such as a prototype device) satisfies the Design Input requirements.

iv. Verification Protocols and Verification Test (or Analysis) Reports are maintained under Document Control in the Design History File.

c. Exercises

i. Produce a section of a Verification Protocol document for the ECG system, describing the test procedure(s) to be followed for one or more characteristics of the device, to show that one or more specified requirements of the assumed Design Input have been met by the assumed Design Output.

ii. Conduct a Verification Test of the ECG system in accordance with the Verification Protocol and record the result in a section of a Verification Test Report.

d. Example

i. Verification Protocol for ECG (section)

(1) Using a frequency signal generator, input sine waves of constant known peak voltage amplitude (for example, 0.1 volt) with frequencies of 0.1, 1.0, and 10.0 Hz into the ECG measurement system. Record the frequency and peak voltage amplitude displayed in the ECG output. Compare input and output waveforms on an oscilloscope or other measurement/display system and record whether or not the output waveforms faithfully reproduce the input waveforms.

ii. Verification Report for ECG (section)
Output waveforms faithfully reproduce the input waveforms.

Frequency (Hz)		Amplitude (v)	
Input	Output	Input	Output
0.1	0.1	0.1	0.1
1.0	1.0	0.1	0.1

10.0	10.0	0.1	0.1

e. Additional references/resources: None

7. Lesson 7: Validation Protocols and Verification Tests and Evaluations.
   a. Summary
   b. Design Validation is the establishment by objective evidence that device specifications conform with user needs and intended use(s).
   c. Critical teaching points
   d. Reading assignment - read before lesson
      LG: Section II.9 and II.10
      DCG: Section G, Design Validation
   e. Design Validation consists of the total set of Validation Tests and Evaluations with their respective Validation Protocols, and is intended to ensure that devices meet defined user needs and intended uses.
   f. Each Validation Test or Evaluation is conducted in accordance with a Validation Protocol that is written, approved, and placed under document control before the Validation Test or Evaluation begins.
   g. Validation Tests and Evaluations are required to use devices made under defined operating condition using production methods.
   h. Validation Tests and Evaluations must include tests of the device under actual or simulated use conditions.
   i. For devices including software, Validation Tests and Evaluations must include software validation and risk analysis.
   j. Results of each Validation Test or Evaluation is recorded in a dated, signed Report that is included in the Design History File.
   k. Exercises
   l. Suggest a validation test for an implantable pacemaker that is not a clinical use or trial.
   m. Example
   n. A validation test of an implantable pacemaker that is not a clinical use or trial must show whether or not the device meets user needs and intended uses. To accomplish this, a suggested validation test may consist of implants of the device in animals such as sheep or pigs.
   o. Additional references/resources: None

8. Lesson 8: Labeling and Packaging.
   a. Summary
   b. Medical devices cannot be lawfully marketed without appropriate Labeling in accordance with regulations. For sterile products, the Packaging must maintain sterility, while for all devices, the Packaging must provide protection during shipment.
   c. Critical teaching points
   d. Reading assignment - read before lesson
      LG: Section II.11 and Section III.5
   e. Labeling is required by FDA regulations. Labeling for a device includes a description of the device (its type), its sterile (or non-sterile) condition as supplied to the user, its size, the manufacturer's (or distributor's) name, address, and telephone number, lot and/or serial number (when traceability is required), expiration date (use-by date for a sterile device), and instructions for use.

f. Packaging must protect the device and, for sterile devices, maintain its sterility. Packaging must protect the device from drops and sudden accelerations or decelerations, and from changes in temperature or air pressure, that may occur during shipping. This is often accomplished by placing the device in an inner container that is placed within a shipping box, and the space between is filled with shock-absorbing protective materials. For sterile devices, the inner container often may consist of or include nested sterile packaging. The outer sterile pack of the nest is to be opened by a scrub nurse in an operating room, allowing the inner sterile pack to be dropped onto the sterile field.
g. Exercises
h. Describe the labeling items required for an air flow transducer to be used in a spirometer.
i. The Instructor and Students may choose to describe the labeling for a relevant medical device.
j. Example
k. Labeling Items for a Spirometer Air Flow Transducer
l. Device Name: Air Flow Transducer for Spirometer
m. Sterile Condition: (Non-sterile)
n. Manufacturer or Distributor Name, Address, and Phone Number
o. Lot or serial number
p. Expiration date: (Not applicable)
q. Additional references/resources: None

9. Lesson 9: *Transfer to Manufacturing and Process Validation.*
a. Summary
b. A carefully executed Transfer to Manufacturing is a critical for the production of commercial devices that conform to the Design Output.
c. Because it is often not feasible (either technically, economically, or both) to fully inspect the results of a manufacturing process, Process Validation is used to assure that the results consistently meet specifications.
d. Critical teaching points
e. Reading assignment - read before lesson
LG: Section II.13, II.14, and Section III.6
DCG: Section H, Design Transfer
f. Transfer to Manufacturing requires the development of documented manufacturing processes that can reliably produce devices that conform to the Design Output specifications for commercial distribution. Since manufacturing processes used for producing large quantities may differ from those used for producing the smaller quantities typically required for Design and Development Project activities, careful attention must be paid to assure the faithful and reliable production of product within specifications. Realistic manufacturing tolerances and their effects on product fit, form, and function should be considered (including by Risk Analysis - FMEA) as early as possible in the Design and Development Project to assure an efficient Transfer to Manufacturing and consistent product quality. Often, manufacturing engineer(s) or other production staff on the Project Team assist in the definition of realistic manufacturing tolerances and develop and document manufacturing procedures.
g. A Process Validation is required whenever the result of the manufacturing process cannot be fully verified by subsequent inspection and testing. A common example is sterilization: to perform microbiological testing, the product sterile packaging must be opened.
h. Process Validation generally requires statistical reasoning and methods. Often, Process Validation involves statistical methods of sampling product from a number of production lots.

Another frequently used statistical method is the model study, in which product samples are obtained from the process operated at each of a number of predetermined settings within (and sometimes beyond) the range of specified production operating settings.

i. For sterilization, special methods are used for Process Validation. In one method, test samples are created by sequestering microbial spores on paper strips in product regions judged difficult for the sterilizing agent to penetrate. A predetermined number of such products are then packaged and sterilized using the production method (which may include placement of the test sample within a lot or pallet of packaged product). After sterilization, the test samples are opened and the spores placed in a microbial growth medium. If the spores do not grow into bacteria, the sterilization is considered validated.
j. Exercises
k. List several features or properties of mass-produced EEG electrodes that are not likely to be fully inspected and therefore would be candidates for process validation.
l. The Instructor and Students may choose other relevant device products and identify features or properties that would be candidates for process validation.
m. Example
n. Features of EEG Electrodes Likely Requiring Process Validation
o. Sterility
p. Adhesion
q. Composition
r. Conductivity (possibly)
s. Dimensions (possibly)
t. Additional references/resources: None

10. Lesson 10. *Regulatory Submissions and Clinical Investigations*
    a. Summary
    Within the US, medical devices require FDA approval prior to sale.
    b. Critical teaching points
    c. Reading assignment - read before lesson
    LG: Sections I.8, I.9, I.10, and Sections II.15, II.16
    www.fda.gov/cdrh/devadvice/pma
    www.fda.gov/cdrh/devadvice/314
    www.fda.gov/cdrh/devadvice/ide
    d. Device class determines the type of regulatory submission needed.
    New or modified Class I and II medical devices require Premarket Notification (510(k)) clearance from FDA to be marketed in the US. Modifications of Class I and Class II devices that significantly affect safety and effectiveness require 510(k) clearance. A few very low-risk devices, listed by FDA, do not require 510(k) clearance. New or modified Class III medical devices require an FDA-approved Premarket Approval (PMA) or PMA Supplement, respectively. Some new or modified devices require clinical investigations (studies in patients) to gather safety and/or effectiveness data for submission; an Investigational Device Exemption (IDE) is required to allow such studies. The FDA lists the class of many devices at its web site.
    e. Device market and regulatory history helps determine the type of regulatory submission needed.
    Class III devices that were legally marketed in the US before May 28, 1976, including devices substantially equivalent to such devices, and for which FDA has not published a notice that Premarket Approval is required, may be cleared for market through the Premarket

Notification process (510(k)). An example of such a device is the implantable heart pacemaker.

f. A company decides on submission type based on regulations.
A company's Regulatory Affairs Department (or equivalent) must decide, based upon FDA regulations, whether a new or modified medical device that is intended for sale in the US should be cleared through the FDA using the Premarket Notification (510(k)) procedure or the Premarket Approval (PMA) procedure. Also, Regulatory Affairs must decide whether to a clinical investigation is needed for the new or modified product; if it is, then the company must obtain an Investigational Device Exemption (IDE).

g. FDA may accept or reject a company's 510(k) submission.
If a company has submitted a 510(k) for a device, but FDA finds that the device is not substantially equivalent to the claimed predicate device, the FDA will so notify the company. The company must then submit a 510(k) with new information, file a PMA, or petition the FDA for reclassification of the device.

h. FDA may accept, conditionally accept, or reject a company's PMA (or PMA Supplement, or PMA Amendment, or PMA Supplement Amendment) submission.
FDA conditional approval allows marketing of the device only if the company fulfills certain conditions, such as post-marketing surveillance. A company may respond to an FDA non-approval (rejection) letter by submitting new information in a PMA (or PMA Supplement) Amendment.

i. Exercises

j. Produce a report assessing the kind of Regulatory Submission (510(k), PMA, PMA Supplement, Petition for Reclassification) required for a medical device and whether a clinical investigation (IDE) would be required, and provide reasons for these assessments, assuming:

k. It is a new implantable Left Ventricular Assist Device, which helps pump blood in persons with damaged hearts otherwise incapable of maintaining sufficient cardiac output; there are no such devices previously or currently marketed in the US.

l. It is a modification of your company's implantable defibrillator, which electrically shocks the left side of a fibrillating heart; FDA has previously approved your company's application for Premarket Approval for the defibrillator, but now your company has developed and wishes to distribute with the defibrillator more efficient electrodes than were available originally.

m. It is a new Class III device, and there are other devices with similar technologies and intended uses currently legally marketed in the US under PMA approval.

n. It is a new Class II device, and there are other devices with similar technologies and intended uses currently legally marketed in the US under 510(k) approval.

o. It is a modification, significantly affecting safety or effectiveness, of a device that has been previously legally marketed in the US by your company under premarket notification.

p. The Instructor and Students may construct other exercises that point out the regulatory submission paths for medical devices; a useful resource to formulate examples is the FDA web site cited in the Additional references/resources.

q. Examples

r. A new device such as a Left Ventricular Assist Device that is critical to supporting life would be placed into Class III and would require a PMA; also, a clinical investigation would be needed to show safety and effectiveness, so an IDE would be required.

s. A modification of a device such as a defibrillator approved by PMA requires a PMA Supplement for approval. An IDE may be required to conduct a clinical investigation to show the safety and effectiveness of the modification.

t. A new Class III device requires a PMA application, unless it belongs to the small group of

Class III devices legally marketed in the US prior to May 28, 1976 for which FDA has not yet called for PMA submissions, in which case it requires a 510(k). If other similar devices have been approved by the PMA process, then the new device must also follow the PMA process. The company sponsoring the new device may petition FDA to reclassify the generic device type from Class III to Class II; if FDA approves the petition, which it sometimes does if the device type historically appears to have a relatively low level of risk, the company and all subsequent applicants may use the premarket notification process.

u. A new Class II device requires premarket notification (510 (k)).

v. A modification to a device that significantly affects device safety and effectiveness, for a device that has been marketed in the US under premarket notification (510(k)), requires a 510(k) clearance.

w. Additional references/resources
An efficient way to find the FDA Class and submission path (510(k) or PMA) for a device is to do a search for it (by generic device type) at:
www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm

V. References

1. *Design Control Guidance for Medical Device Manufacturers,* Center for Devices and Radiological Health, FDA, March 11, 1997
www.fda.gov/cdrh/comp/designgd
2. *Do It By Design: An Introduction to Human Factors in Medical Devices,* Center for Devices and Radiological Health, FDA, December, 1996
www.fda.gov/cdrh/humfac/doit
3. *Quality System Information for Certain Premarket Application Reviews: Guidance for Industry and FDA Staff,* Center for Devices and Radiological Health, FDA, February 3, 2003
www.fda.gov/cdrh/comp/guidance/1140.pdf
4. *Failure Modes and Effects Analysis (FMEA),* Crow, Kenneth, DRM Associates;
www.npd-solutions.com/fmea