LEARNING OBJECTIVES

1. To review the fundamental concepts of premarket regulatory activities of medical devices in the United States
2. To apply the regulatory concepts to an infusion pump device
3. To identify the available regulatory pathways for medical devices

TOPICS

Medical device definitions; device classifications; regulatory pathways

ASSUMPTIONS

The case study is based on the following assumptions:

- Target audience is undergraduate/graduate students who have no experience in the medical device industry.
- Students are expected to work on the case before, during, and after class (3–4 hours of homework).
- Users of the case study are instructors who may have some knowledge of the U.S. Food and Drug Administration (FDA) and its Web site.
- Instructors may spend 3–4 hours to teach the materials involved in the case study.

Instructors should—

- Be familiar with the reference materials listed.
- Be proficient in searching FDA’s Web site and use the site for class demonstration.
- Dedicate sufficient preparation time for class sessions and to review the reference materials and Web site.
- Prepare, engage, and immerse students in the lessons learned from the case study.
- Instruct students to be prepared at least 2 weeks before Session 1.
- Instruct students to obtain hands-on experience in searching device information from Center for Devices and Radiological Health (CDRH) databases during Session 1.
- Involve students in class discussion to identify a regulatory pathway for the device during Session 2.

SUGGESTED APPROACH

1. Preparing Students (Session 1: Before Class):
   Students are expected to read the case study and other materials and complete assigned activities before Session 1.

2. Engaging Students (Session 1: In Class):
   This session is a lecture. It ideally features a demonstration of how to surf CDRH’s databases, exercises to find product information, and a discussion of infusion devices.

3. Immersing Students (Session 2): This session emphasizes group discussion on choosing a regulatory pathway for the case. Students are expected to complete assigned activities before Session 2.
STUDENT ACTIVITIES

SESSION 1: BEFORE CLASS

I. Review the following CDRH Learn videos:

1. Overview of Regulatory Requirements: Medical Devices
   (approximately 30 minutes)
   a. [Link](http://fda.yorkcast.com/webcast/Viewer/?peid=040308365ec8405bad39b06de8561bd1d)

2. The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications or 510(k)s
   (approximately 1 hour)
   a. [Link](http://fda.yorkcast.com/webcast/Viewer/?peid=f59814465f674e59a19f3b61c6880ea81d)
   b. [Link](http://fda.yorkcast.com/webcast/Viewer/?peid=e0ea02ad4f0c4532a89fa946c0a1d0)
   c. [Link](http://fda.yorkcast.com/webcast/Viewer/?peid=2360fd6ad7468aeabd0431f76ace)

3. The Investigational Device Exemption (IDE) Process
   (approximately 1 hour)
   a. [Link](http://fda.yorkcast.com/webcast/Viewer/?peid=8553ad7df9054fe6e6f004b359ad1e1d)
   b. [Link](http://fda.yorkcast.com/webcast/Viewer/?peid=46344ca5abbb465e88404a92eed542f71d)

II. Answer the following questions:

1. What is the definition of a medical device according to the Federal Food, Drug, & Cosmetic (FD&C) Act?

   The term “device” means an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is—

   a. Recognized in the official National Formulary, the United States Pharmacopeia, or any supplement to them

   b. 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

   c. 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

   d. Not dependent upon being metabolized for the achievement of its primary intended purposes.

2. Give three examples of medical devices you have seen in a pharmacy or hospital.

   Pharmacy:
   a. Class I: bandage, condom, thermometer, ear wick, weight scale
   b. Class II: blood pressure monitor, humidifier, hearing aid, blood glucose test system
   c. Class III: N/A
Hospital:

a. Class I: tongue depressor, patient bed, stethoscope
b. Class II: X-ray system, most imaging systems, suture kit, surgical mask, oximeter, electrocardiograph
c. Class III: coronary stent

3. Name and describe the ways in which a medical device company may obtain “clearance” of its product before putting it into commerce.

The Medical Device Amendments (MDA) (Pub. L. 94–295) to the FD&C Act were enacted on May 28, 1976. The MDA directed FDA to issue regulations that classified all devices in commercial distribution at that time into one of three regulatory control categories, Class I, II, or III, depending upon the degree of regulation necessary to provide reasonable assurance of their safety and effectiveness. The class into which a device is placed determines the requirements that a medical device manufacturer must meet prior to distributing a device in interstate commerce. According to section 513(a)(1) of the FD&C Act (21 U.S.C. § 360c(a)(1)), the three device classes are defined as follows:

Class I: Devices are subject to a comprehensive set of regulatory authorities called general controls that are applicable to all classes of devices.

Class II: Devices for which general controls, by themselves, are insufficient to provide reasonable assurance of the safety and effectiveness of the device, and for which there is sufficient information to establish special controls to provide such assurance.

Class III: Devices for which general controls, by themselves, are insufficient and for which there is insufficient information to establish special controls to provide reasonable assurance of the safety and effectiveness of the device. Class III devices typically require premarket approval.

Premarket notification is the process by which a new device, i.e., a postamendments device, is classified into one of these three device classes. A manufacturer who intends to market in the United States a Class I, II, or III device intended for human use, for which a premarket approval application (PMA) is not required, must submit to FDA a premarket notification submission, often referred to as a 510(k), unless the device is exempt from the 510(k) requirements of the FD&C Act and does not exceed the limitations of exemptions for each of the device classification regulations (Section .9 of 21 CFR Parts 862 through 892, e.g., 21 CFR 862.9, 21 CFR 864.9).

Under section 510(k) of the FD&C Act, a manufacturer must submit a 510(k) to FDA at least 90 days before introducing, or delivering for introduction, a device into interstate commerce for commercial distribution. The Agency determines whether or not the device meets the criteria for market clearance (sections 510(k) and (n) of the FD&C Act (21 U.S.C. §§ 360(k) & (n))). The Agency bases its decision on whether the device is substantially equivalent to a legally marketed predicate device (section 513(i) of the FD&C Act (21 U.S.C. § 360c(i))).

A medical device may be cleared for market (distribution into interstate commerce for commercial use) by demonstrating substantial equivalence to a legally marketed predicate device.
4. Name and describe the ways in which a medical device company may obtain “approval” of its product before putting it into commerce.

PMA is the FDA process of scientific and regulatory review to evaluate the safety and effectiveness of Class III medical devices. Class III devices are those that support or sustain human life, are of substantial importance in preventing impairment of human health, or present a potential, unreasonable risk of illness or injury. Due to the level of risk associated with Class III devices, FDA has determined that general and special controls alone are insufficient to assure their safety and effectiveness. Therefore, these devices require a PMA application under section 515 of the FD&C Act in order to obtain marketing authorization. In many cases, device development and evaluation include clinical investigation. Manufacturers or sponsors may initiate clinical investigations in the United States to evaluate medical devices under FDA’s IDE regulations, 21 CFR Part 812. FDA approval of an IDE submission allows the initiation of a clinical investigation of a significant risk device.

III. References

Note: Draft guidances are subject to change and are not for implementation.

1. The FD&C Act

2. Subchapter II—Definitions (§ 321; pg 32, paragraph h)

SESSION 1: IN CLASS

I. Access medical device databases
   http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Databases/default.htm
   1. Product classification database
   2. 510(k) database
   3. PMA database
   4. Adverse events database

II. Questions for in-class discussion:

1. What are the three major problems of infusion pumps?
   Software defects, user interface issues, and mechanical or electrical failures.

2. Name all the product codes of infusion pumps.
   Search “infusion.” There are 28 product codes.
3. Identify the potential product code of Neyhard’s device and its likely regulation.

Of the 28 product codes, there is only one code, LZG, for insulin infusion pumps. The governing regulation for LZG is 21 CFR Part 880.5725.

4. What is the potential product classification of Neyhard’s invention?

Class II.

5. What are the likely top three issues for Neyhard’s predicate device(s)?

Parts or components “bent” (34 reports), “dislodged or dislocated” (34 reports), and “kinked” (22 reports).

III. References:

1. Infusing Patients Safely: Priority Issues From the AAMI/FDA Infusion Device Summit

2. Infusion Pump Improvement Initiative
   http://www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/GeneralHospitalDevicesandSupplies/InfusionPumps/UCM206189.pdf

SESSION 2:

I. Complete the following before class:

   1. Review the IDE, PMA, and 510(k) processes.
      
      See references 1–6.

   2. Determine the intended use of Neyhard’s infusion device.

   Use the identified product code to obtain information.

   Product Code: LZG

   Intended Use: Sec. 880.5725 Infusion pump

   a. Identification: An infusion pump is a device used in a health care facility to pump fluids into a patient in a controlled manner. The device may use a piston pump, a roller pump, or a peristaltic pump and may be powered electrically or mechanically. The device may also operate using a constant force to propel the fluid through a narrow tube which determines the flow rate. The device may include means to detect a fault condition, such as air in, or blockage of, the infusion line, and to activate an alarm.

   b. Classification: Class II (performance standards)

   3. Identify general controls and special controls, and give examples.

   Premarket notification is a regulatory control and is part of the so-called General Controls. General Controls also include Establishment Registration, Medical Device Listing, Manufacturing of Medical Devices in accordance with Current Good Manufacturing Practices (CGMP 21 CFR Part 820), and Labeling Medical Devices in accordance with labeling regulations in 21 CFR Part 801 or 809. Special Controls include special labeling requirements, mandatory performance standards, and postmarket surveillance, e.g., biocompatibility, ensuring compatibility with the tubing and the insulin infusion, human factors testing.
II. Questions for in-class discussion:

1. Propose the best pathway for Neyhard to present to his potential investors.

   Premarket notification, or 510(k), is the best pathway for Dr. Neyhard.

2. Justify your proposed pathway.

   a. Technologically capable: Dr. Neyhard could design a device similar to those in the market.
   b. Least burdensome: Information related to device performance, field events, use performance, and regulatory submissions is publicly available. The team would spend less effort to obtain clearance from FDA.
   c. Shortest time: 510(k) would take much less time to obtain clearance from FDA. Estimated time for 510(k) is 90–150 days; for PMA, 180–210 days.
   d. Relatively economical: The review fees for 510(k) and PMA submissions are shown on the following page.

The applicable fee corresponds with the date of receipt of the submission by FDA. FDA will consider the submission incomplete and will not accept it for filing until the fee is paid in full. That is, the date of receipt is the date that the submission has been received AND the fee is paid in full.

3. How would you determine whether there is a need for clinical evaluations?

   PMA submission requires the evaluation of safety and effectiveness of a medical device; thus, clinical evaluation is necessary. Premarket notification or 510(k) requires the demonstration of substantial equivalence of a medical device to a predicate(s); therefore, consider assessing the following:

   a. Intended use
      i. Deviation(s) from predicate device
   b. Technological characteristics affecting user requirements or device performance but not different types of safety and effectiveness questions. Provide the data to demonstrate that this device performs substantially equivalent to the predicate.
      i. Materials used (e.g., biocompatibility, local or foreign source)
      ii. Energy employed (e.g., electrical, mechanical, or chemical)
      iii. Information processed (e.g., software controlled, dosage accuracy)
      iv. Performance/storage environment defined
c. Usability factors affecting user requirements or device performance but not different types of safety and effectiveness questions.
   
i. Target population (e.g., infant, adult, aged)
   
ii. User friendliness (e.g., left/right handed, big/small sized, legibility/readability)
   
iii. Environmental specifications (e.g., transit, transportation, storage)
   
iv. Instruction for use (e.g., understandable, length, legible)

### 510(k): FY2013 Device Review User Fees

<table>
<thead>
<tr>
<th>Submission</th>
<th>Standard Fee</th>
<th>Small Business Fee*</th>
</tr>
</thead>
<tbody>
<tr>
<td>510(k)</td>
<td>$4,960</td>
<td>$2,480</td>
</tr>
<tr>
<td>513(g)</td>
<td>$3,348</td>
<td>$1,674</td>
</tr>
</tbody>
</table>

*≤$100 million in gross receipts or sales

### PMA: FY2013 Device Review User Fees

<table>
<thead>
<tr>
<th>Submission</th>
<th>Standard Fee</th>
<th>Small Business Fee*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premarket Application (PMA), Product Development Protocol, Biologics License Application, Premarket Report (for a reprocessed device)</td>
<td>$248,000</td>
<td>$62,000</td>
</tr>
<tr>
<td>First PMA submission from firms with gross receipts or sales ≤$30 million</td>
<td>Not applicable</td>
<td>Fee is waived</td>
</tr>
<tr>
<td>Panel-track Supplement</td>
<td>$186,000</td>
<td>$46,500</td>
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<tr>
<td>BLA Efficacy Supplement</td>
<td>$248,000</td>
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<tr>
<td>180-day Supplement</td>
<td>$37,200</td>
<td>9,300</td>
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<tr>
<td>Real-time Supplement</td>
<td>$17,360</td>
<td>$4,340</td>
</tr>
<tr>
<td>Annual Report</td>
<td>$8,680</td>
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<tr>
<td>30-day Notice</td>
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<td>$1,984</td>
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</tbody>
</table>

*Tables list fees for 2013; fees change annually. For current fees, see Premarket Notification [510(k)] Review Fees and PMA Review Fees.

The small business provision would actually be something to consider discussing with the students as that would be a huge advantage; also, if the device is intended solely for a pediatric population, then the fees are waived. In addition, de novo submissions do not have any fees associated with them.
4. Justify your decision to do or not do clinical evaluations(s).

*Clinical evaluation in the 510(k) process should be—*

- To ensure device meets user requirements;
- To demonstrate continued conformance with a special control or recognized standard.

5. Share the lessons you have learned from the case.

*Capability lessons—regulatory pathways and their related body of knowledge, ProCode, databases, regulations, glossary and terminology, etc.*

*Behavioral lessons—early considerations of regulatory strategy may influence the medical device strategic development plan, regulatory pathway may influence technology chosen for product design and willingness to learn and use FDA databases.*

III. References

*Note: Draft guidances are subject to change and are not for implementation.*

1. The New 510(k) Paradigm

2. Total Product Life Cycle: Infusion Pump—Premarket Notification [510(k)] Submissions

3. 510(k) “Substantial Equivalence” Decision Making Process
   http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/ucm134783.htm

4. FDA Decisions for IDE Clinical Investigations

5. IDE for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human Studies

6. PMA

7. Medical Device Classification Product Codes

8. Requests for Feedback on Medical Device Submissions: The Pre-Submission Program