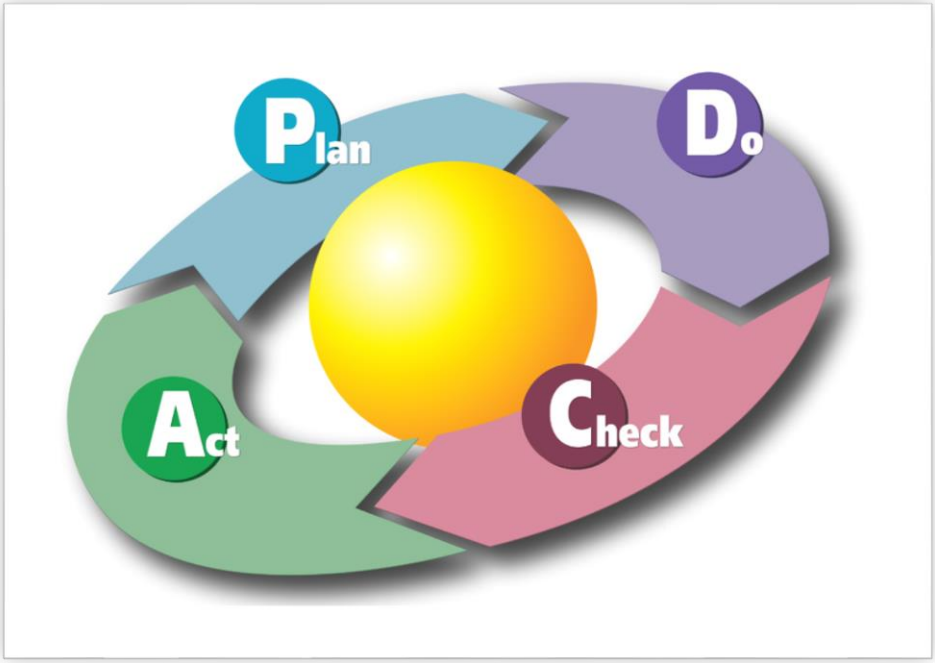

Quality Assurance & Regulatory Affairs for the Biosciences

BITC1340 COURSE TEXTBOOK - 2018

Austin Community College, Biotechnology Program

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Table of Contents

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RESOURCE MATERIAL:

The best and most reliable resource of biotechnology regulations in the US is the Food & Drug Administration (FDA) website. The FDA website is consumer and layman-friendly, up-to-date, and easy to navigate. The majority of the information in this workbook was guided from the FDA website and the book *"Fundamentals of US Regulatory Affairs,"* published by Regulatory Affairs Professional Society (RAPS). Works cited are found at the end of the eBook. The following is a brief list of resource material you may find useful.

1. FDA: http://www.fda.gov
2. Drug Development: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/default.htm
3. CDRHLearn: http://www.fda.gov/Training/CDRHLearn/default.htm
4. Clinical Trials: https://clinicaltrials.gov/
5. RAPS. *Fundamentals of US Regulatory Affairs*, 9th edition. 2015.
6. International Organization for Standardization: http://www.iso.org
7. Donna CS summers, Quality, 5th edition. 2010. Pearson Education. ISBN:978013159249
8. American Society of Quality website: http://asq.org

CHAPTER 1: INTRODUCTION TO BIOTECHNOLOGY & QUALITY ASSURANCE

OBJECTIVES

- ✓ Define Biotechnology
- ✓ Describe the responsibilities of departments in a biotechnology company
- ✓ Distinguish between quality assurance and quality control job functions
- ✓ Identify potential Biotechnology jobs in our community
- ✓ Discuss quality as it relates to the customer
- ✓ Understand the importance of a company vision and mission statement
- ✓ Understand the basis for the importance of quality in a company

INTRODUCTION TO BIOTECHNOLOGY

What is Biotechnology? In the broadest sense, biotechnology is the practice of selecting, manipulating and altering living organisms and their biological processes to produce a product for human benefit. The use of yeast as the catalyst of fermentation when brewing beer, for example, could be said to represent one of humankind's first intuitive steps towards the idea of using biological organisms as tools.

Biotechnology as we know it today focuses on engineering the desired changes in an organism at the genetic level. This type of research and development aims to produce new and improved products and processes in fields such as diagnostics, agriculture, biopharmaceutical, environmental science, and forensics. A medical biotechnology company, for instance, may engineer a virus to produce copies of a particular human gene to be used in gene cell replacement therapy (a type of treatment targeted towards inherited genetic disorders, such as Cystic Fibrosis). Likewise, drought resistant crops and oil-consuming microbes are also common examples of genetically engineered products brought to market by agricultural and environmental biotech companies.

New approaches to Biotechnology: Watch this video! Press control and click on the following link: 3D BioPrinting video
http://www.abc.net.au/news/2016-12-28/scientist-hope-cell-printer-can-be-used-to-make-hearts/8134974

3-D Bio-printing a human ear

TEST YOUR KNOWLEDGE!

1. In your own words, define biotechnology
2. Can you think of a biotechnology product that has improved your life? What makes it a biotechnology product

Biotechnology as a Modern Industry: In the United States alone, there are over 1,800 biotechnology companies in operation representing a growth industry of $100 billion in annual revenues (Earnest & Young Biotech Industry Report 2013). The field continues to diversify as more industries turn to biotechnology for solutions. However, the leaders and innovators in the field remain concentrated within health care, agriculture and environmental biotechnology. Below is an excerpt from Bio.org that discusses the ever-expanding applications of Biotechnology in healthcare, agriculture, and energy.

Biotechnology: Healing, Fueling, and Feeding the World (bio.org, 2014)**.** *At its simplest, biotechnology is technology based on biology - biotechnology harnesses cellular and biomolecular processes to develop technologies and products that help improve our lives and the health of our planet. We have used the biological processes of microorganisms for more than 6,000 years to make useful food products, such as bread and cheese, and to preserve dairy products.*

Biotechnology is a multidisciplinary field, drawing upon the life sciences (e.g., biology) as well as the physical sciences (e.g., chemistry). This 30-minute video (https://youtu.be/yS_rg7rzkSQ) provides a more extensive explanation of Biotechnology, and the basic principles involved. Modern biotechnology provides breakthrough products and technologies to combat debilitating and rare diseases, reduce our environmental footprint, feed the hungry, and use less and cleaner energy, and have safer, cleaner and more efficient industrial manufacturing processes.

Currently, there are more than 250 biotechnology healthcare products and vaccines available to patients, many for previously untreatable diseases. More than 13.3 million farmers around the world use agricultural biotechnology to increase yields, prevent damage from insects and pests and reduce farming's impact on the environment. In addition, more than 50 biorefineries are built across North America to test and refine technologies to produce biofuels and chemicals from renewable biomass, which can help reduce greenhouse gas emissions. Recent advances in biotechnology are helping us prepare for and meet society's most pressing challenges.

Heal the World (bio.org, 2014)**.** ***https://www.bio.org/healthcare*** *Biotech is helping to heal the world by harnessing nature's own toolbox and using our own genetic makeup to heal and guidelines of research by:*

- *Reducing rates of infectious disease;*
- *Changing the odds of serious, life-threatening conditions affecting millions around the world;*
- *Tailoring treatments to individuals to minimize health risks and side effects;*
- *Creating more precise tools for disease detection; and*
- *Combating serious illnesses and everyday threats confronting the developing world.*

Fuel the World (bio.org, 2014). https://www.bio.org/industrial-environment *Biotech uses biological processes such as fermentation and harnesses biocatalysts such as enzymes, yeast, and other microbes to become microscopic manufacturing plants. Biotech is helping to fuel the world by:*

- *Lowering the temperature for cleaning clothes and potentially saving $4.1 billion annually;*
- *Reducing use of and reliance on petrochemicals;*
- *Using biofuels to cut greenhouse gas emissions by 52% or more;*
- *Decreasing water usage and waste generation; and*
- *Tapping into the full potential of traditional biomass waste products.*

Feed the World (bio.org, 2014)**.** *https://www.bio.org/food-agricultural-biotechnology Biotech improves crop insect resistance, enhances crop herbicide tolerance and facilitates the use of more environmentally sustainable farming practices. Biotech is helping to feed the world by:*

- *Generating higher crop yields with fewer inputs;*
- *Lowering volumes of agricultural chemicals required by crops-limiting the run-off of these products into the environment;*
- *Using biotech crops that need fewer applications of pesticides*
- *Developing crops with enhanced nutrition profiles that solve vitamin and nutrient deficiencies;*
- *Producing foods free of allergens and toxins such as mycotoxin; and*
- *Improving food and crop oil content to help improve cardiovascular health.*

Let's Explore!

Go to the BIO.org website and explore! Did you discover anything interesting?

What is their mission?

THE STRUCTURE OF A BIOTECHNOLOGY COMPANY

A typical biotechnology company will employ an array of people with credentials and experience in these disciplines. These scientists and technicians may work in a laboratory setting performing research while others may lend their expertise to other departments such as Production, Quality Control or even Marketing. The type and number of specialized departments within a biotechnology company, as well as the manner in which talent is distributed across them, depends on the type of company it is (agricultural, medical, environmental and so on) and whether it is marketing a service or a product. Let's take a closer look!

The Research and Development (R&D) Department: In these laboratories, you will find Research Scientists working alongside technicians towards a common goal: to create new products and processes and improve upon existing ones. The R&D Department is where the majority of creative problem solving takes place. In some companies, Research is split off from Development. In that instance, the Research Department focuses on the discovery of new products and processes, while the Development department helps transition the discoveries from the research phase into the product production phase.

R&D Responsibilities

1. Discovery – Investigate a potential product with commercial value
2. Characterize the properties of the product; physical properties, safety
3. Establish product specification based on customer expectation
4. Establish testing and documentation procedures
5. Establish product stability and shelf-life
6. Develop a production plan, including scale-up

The Production Department: Once a product has been tested, tweaked and scaled, it becomes the responsibility of the Production Department to manufacture it. Production requirements will depend on the type of product being manufactured. At a medical biotechnology company, the Production department may resemble a large-scale laboratory if the products in production, say a bacterium, for example, are grown as cultures. In a company producing medical equipment, the production department is more likely to resemble a clean-room with people and machinery working together to assemble the parts. Job titles in this area might be Manufacturing Operator, Technician or Supervisor, Production Technician or Pilot Plant Operator or Technician.

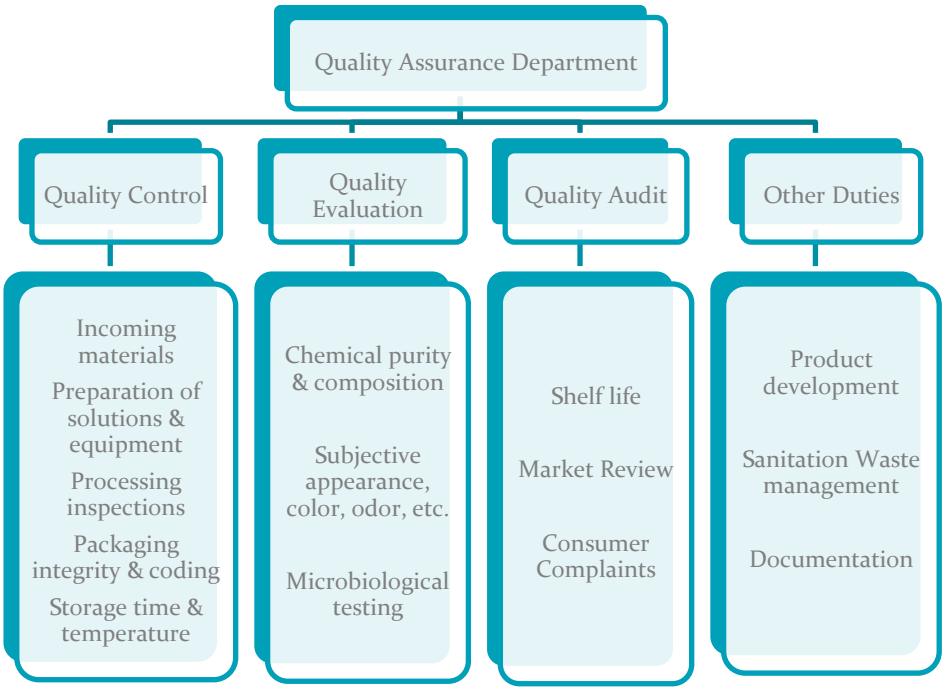
Production Responsibilities
1. Manufacture the product
2. Work with large scale production equipment
3. Monitor production process and initiate corrective action when needed
4. Clean, calibrate and maintain production equipment
5. Follow all documented procedures

The Quality (QA/QC) Department: The Quality Department establishes guidelines to monitor manufacturing processes, and examining in-process and finished products to ensure adherence to quality standards. These tasks are typically split across two departments: Quality Assurance and Quality Control. Quality Control is responsible for monitoring. They perform the laboratory testing, environmental monitoring, and in-process sampling. Quality Assurance refers to the quality system responsible for overseeing the process. The Quality department will work closely with every other department within the company, as well as legal agents outside the company such as auditors, inspectors, and FDA.

Quality Control	Quality Assurance
1. monitor equipment, environment, personnel, and product	1. review all production procedures
2. test samples of the product and the materials that go into making the product to determine whether they are acceptable	2. ensure that all documents are accurate, complete, and available
3. compare data to established standards	3. decide whether or not to approve the product for release to consumers
	4. review customer complaints

Quality Department Organization: The diagram below shows the typical organization of a Quality department for a biomanufacturing company. *Exact organization and responsibilities vary with the type of company, product and the regulatory standards required of a product*, but the general concerns listed are common to all manufacturers. Obviously, QA and QC are intertwined and dependent on each other and why most companies, especially small-to-mid-sized biotechnology companies, combine QA and QC into a single department.

Quality Control (QC): QC has a limited function in the company and is responsible for the testing or sampling in compliance with the specifications determined by QA. During production, the QC technicians will sample and test at many stages, following the specifications developed during the design phase. They will be trained in appropriate techniques, such as operating equipment and performing assays, and adhering to regulations. They will be monitored and supported by QA who hold the final responsibility for releasing the product. Thus, the QC organization has specific responsibilities that center around following the direction given by the QA organization. These activities are directed toward evaluation of the product and control of the processes used to produce the product.



The typical organization of a QA department for a biomanufacturing company

Quality Assurance: QA is the function that sets up the systems and methods for "assuring" the quality of the product. The product is determined by the methods of manufacture, and quality assurance deals with the manufacturing process to "build quality" into the product through the control, evaluation, and audit of a manufacturing system. The quality assurance department of a manufacturing company is ultimately responsible for all the factors involved to make sure that the customer receiving the product will be satisfied.

QA is a part of the quality of concept and quality of specification subcategories. Quality assurance begins with the design of a product and the process for making it. It is necessary that the product is designed such that it is possible to design a process for making it that is highly dependable and resulting in a highly consistent product. Sometimes such an ideal process is referred to as being "robust," in that the steps leading to the final product are straightforward, easy to monitor, and easy to duplicate from batch to batch. Toward that end, each step of a manufacturing process must have easily measurable parameters that can be monitored to ensure that the material that leaves that stage is within specifications that will allow for a final product of high quality.

When a process is developed for the production of a product, a plan is developed for the quality assurance department to oversee and monitor key steps of the process. This oversight of production is to make sure that the procedures are being followed and carefully documented by production personnel on a routine basis. This will call for a daily oversight and testing of raw materials coming into the process, materials as they are being processed, and final product leaving a process. The process itself is monitored by the QA department by frequent testing and calibration of production and test equipment.

In short, it is the responsibility of the QA department to assure that the plan for making the product works, that the production personnel is complying with the plan and that the product leaving the production facility meets the quality specifications of the product so that the customers are satisfied with the product.

Quality Documentation: The documentation aspect of QA is broad and varied. A well-run company has a clear paper trail for every aspect of production. The following are examples documents that may be maintained by QA.

- Regulations: Responsible for documents demonstrating compliance with regulations
- Training: Responsible for documents pertaining to personnel training.
- QC records: Responsible for documents pertaining to QC testing of the company's products.
- Quality Audits: QA is responsible for all documents pertaining to quality audits.
- Procurement: QA will maintain documents involved in audits of subcontractors and vendors.
- Product Batch Records: Contain all the documents relating to the production of a specific lot batch of a product. This document is just as important as the product itself. It proves how the product was manufactured and that regulations were followed.

For the following tasks identify if they will be done by the quality assurance department or the quality control department.

Process	QA/QC?
Testing raw materials	
Testing final products	
Approving final products for release to customer	
Monitoring equipment in product	
Working with FDA regulatory body	

HOW IS QUALITY INVOLVED COMPANY-WIDE?

A quality product is the result of a quality company involving every member of the company from the shipping and receiving, to marketing, in addition to any of the wet-lab job duties. Below is a brief summary of Total Quality Management in a company. More on this quality philosophy later in the course.

Engineering or Research & Development (R&D): As a rule, new and existing products are designed, redesigned and evaluated by engineering or R&D departments. A company's Quality Department may play an active role in the process in the following ways:

- ✓ Establish safety as a formal design parameter.
- ✓ Review designs for safety at strategic points of the design formation and approval cycle.
- ✓ Verify that the design meets all government and industry standards.
- ✓ Monitor all material and material substitutions to make sure they meet all safety codes.
- ✓ Review the tracking method(s) in place for product traceability.

Marketing (Sales): Product information must be up-to-date and accurate including sales materials and user's manuals. Quality can assist in this area by ensuring that all of the following occur:

- ✓ All sales and marketing material are evaluated for technical and usage accuracy.
- ✓ Products are properly packaged.
- ✓ Products are properly labeled (e.g., with warnings, remedies and storage directions).
- ✓ Everyone involved with the product receives safety information.
- ✓ The user's manual is evaluated for accuracy and clarity.
- ✓ Anyone involved in providing information to end users is properly trained.

Manufacturing: Quality may assist manufacturing in the following ways:

- ✓ Inspect & test product before shipping to confirm that it meets established specifications
- ✓ Provide training for workers to meet safety and quality standards.
- ✓ Audit the manufacturing process
- ✓ Provide feedback to upper management about production and product safety.
- ✓ Document product test results.
- ✓ Ensure calibration of test equipment.
- ✓ Schedule and perform tests. Evaluate results.
- ✓ Make decisions about the fitness of nonconforming products.

The Support Departments: Specialized support departments are an important part of every company. They can include housekeeping, metrology, customer/technical service, shipping & receiving, product filling, sample Assession to name a few.

Support Departments

1. ***Engineering***: Ensures proper installation and operation of equipment & building
2. ***Facility maintenance:*** Typically includes janitorial and maintenance
3. ***Receiving and Shipping***: Handles raw materials and other supplies
4. ***Dispensing***: Package products for consumer use.
5. ***Metrology***: Ensures proper functioning of laboratory instruments.
6. ***Marketing and Sales***: Handles public relations, product branding; marketing materials
7. ***Regulatory Affairs:*** Works to ensure compliance with regulations.

Commercialization. A typical sequence of events in the commercialization of a biotechnology product takes place as in other businesses:

The Path of a Biotechnology Product

1. Ideas
2. Scientific development and market research
3. First production capabilities
4. Testing and approval
5. Marketing and final production

TEST YOUR KNOWLEDGE!

CASE STUDY: A group of scientists at a University has isolated and cloned a human gene that stimulates the DNA repair system in response to UV irradiation. They want to purify it and put into sunscreen products as a way to reduce DNA damage that leads to skin cancer. Luckily, for the scientists, they were able to clone the gene into a bacterial system, and they have developed methods to grow large quantities of these bacteria, harvest the bacteria, and purify the protein. The product is now in Phase III clinical trials, and the results are promising. Review the following list of tasks completed in the company and identify the department responsible for the task.

Job Task	Department Responsible
Devised a method to insert the gene into bacterial cells.	
Manufactured the protein that went into sunscreen lotion.	
Tested the final product to determine if the protein is present in the lotion and at the desired level.	
Take samples from throughout the production facility to test for microbial contaminants.	
Submit forms to the government to request permission to test the compound in human volunteers.	
Sterilize the equipment necessary to mass-produce the protein.	

CAREERS IN BIOTECHNOLOGY

The biotechnology industry has been steadily growing in the Austin area. Today Austin's bioscience community encompasses over 100 companies that employ more than 7000 people in the areas of research, diagnostics, pharmaceuticals and medical devices. Some of these companies include ThermoFisher Scientific, XBiotech, Insys Therapeutics, MyriadRBM, Agilent, Asuragen, Bioo Scientific, Luminex, Spot On Sciences, and TeVido Biodevices to name a few! Austin is also a major contributor to academic research in the biological sciences, both at the University of Texas, Texas State University, and the University of Texas/M.D. Anderson Cancer Research Center in nearby Bastrop.

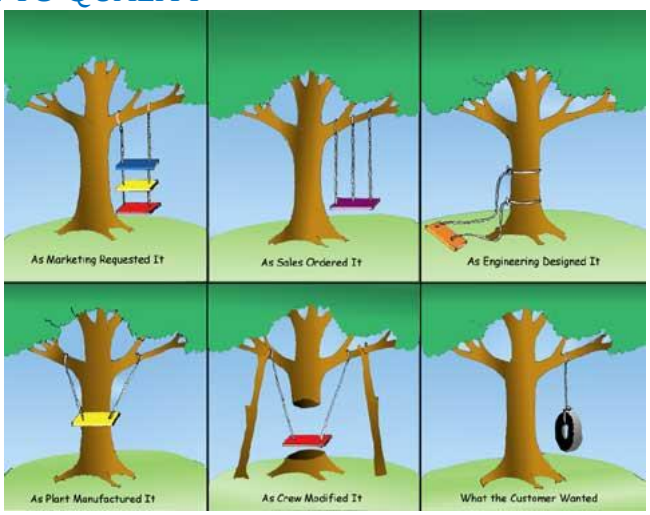
Let's Explore!

Exercise 1: What can you do with a degree in biotechnology? Watch this video of ACC Biotech graduates working in the local biotech industry: https://youtu.be/_vVLfgaDpos

Exercise 2: Exploring a career in the life sciences. To learn more about life sciences, companies in Austin visit the Chamber of Commerce (https://www.austinchamber.com/economic-development/key-industries/life-science/) or visit the websites of any of the companies listed above. To explore jobs nationally, check out a Bio-Link career. Click on "where are biotech employers located." Scroll down and select Texas. Review the companies and Universities that are biotechnology-related employers. Select an Austin, Texas Biotechnology or Life Sciences company that interests you.

A. Write a short bio about the company that you have selected, describing the company's location, its approximate size, and some specific products or services that it markets.

B. Click on "What are some Biotechnology Careers" to learn more about some potential careers in Biotechnology. Pick one that interests you. In your own words, summarize the career and why it interests you.



Tree swing demonstrating Customer Inputs. (Innovations, 2016)

Why is Quality a Necessity? This comic, originally from Don Kite (1970), is funny but brings up an excellent point about quality. *Making the connection between what a customer wants and what a company provides is essential for a successful business.* How does managing quality fulfill customers' needs and expectations? For businesses to succeed in such a competitive and demanding market, they need to formulate a way to do what they do faster, better and cheaper than the competition. Their survival depends on it. Understanding quality and quality systems are what can give businesses the edge they need to succeed and compete.

Quality may mean different things to people. If you asked several people to define quality, you would most likely get different answers because each person values items or processes in their own way. What one person feels is important, another person may not. You have probably experienced this at home or with friends. There are likely different views in your family on how to clean the bathroom and the quality of the cleanliness. ☺

Quality is a Customer Determination: Many prominent contributors in the field of quality use various definitions and meanings of the word Quality. One definition of quality is provided by one prominent quality pioneer, Armand Feigenbaum. In his comprehensive text on the subject, Total Quality Control, Armand states that: *"Quality is a customer determination based on the customer's experience with the product or service, measured against his or her requirements – stated or unstated, conscious or merely sensed, technically operational or entirely subjective – and always representing a moving target in a competitive market."* (Summers, 2010)

Several principles stand out in this view of quality: No two customers will have the same expectation for the same product, and one customer's needs may even change over time as they use the product. Companies must solicit feedback from their customers and respond to their needs even as they change.

- ✓ Customer Determination: Only a customer can decide how well a product meets their needs.
- ✓ Experience: A customer will determine the quality of a product using the product.
- ✓ Requirements: Necessary aspects of the product may be stated or unstated by the customer.
- ✓ Technically operational: Aspects of a product may be clearly identified verbally by the customer.
- ✓ Entirely Subjective: Aspects of a product may be conjured in a customer's personal feelings.

In later chapters, we will discuss the various ways in which companies have used quality systems to help them remain competitive in the global market. Every company establishes a routine way of doing things, but what happens when the way they are doing things no longer works for reasons out of their control? What if the market changes? What happens when the customer needs change? What about the needs of their workforce? How an organization adapts to a rapidly changing market and customer base is crucial to its survival.

Corporate Culture. Corporate culture is an important aspect of a good quality product. A successful company has *a clear vision statement* (how they see themselves in the future) which helps them create a cohesive atmosphere of shared value systems with both their employees and customers alike. *A mission statement* is developed to support the organization's vision. The mission statement should be short, complete and timeless. Many companies incorporate a *values (or philosophy) statement* that relay to the customer core beliefs and guiding principles of the company. Companies will frequently have also a *quality statement* or quality policy outlining their dedication to a quality product.

For the company you chose previously, return to their website and look for statements on company philosophy; vision, mission, quality statement/policy… What did you find?

As a customer or prospective employee, what do you think about these? Do they influence how you feel about purchasing their product or working at their company?

Quality Principles

In the next few chapters, we will investigate different quality philosophies and quality systems. Most quality systems are based on the marriage of two main quality principles; Total Quality Management and Continuous Improvement.

Total Quality Management *(TQM) is a management approach that places emphasis on continuous process and system improvement as a means of achieving customer satisfaction to ensure long-term company success."* (Summers, 2010). TQM is not a temporary fix or used for short-term problem-solving. It is a long-term, deeply committed management style that is dedicated to the improvement of the process on an unwavering commitment to meeting the customers' needs.

*"The **Continuous Improvement** (CI) philosophy focuses on improving processes to enable companies to give customers what they want the first time, every time."* (Summers, 2010) This customer-focused philosophy is a flexible one placing emphasis on customer service, teamwork, and problem-solving.

TQM relies on all members of the company to participate in quality

Quality Systems & Methodologies

Many companies follow quality systems and standards to help them meet the needs of the customer. We will go in depth into the quality methodologies which are important in the biosciences in a later chapter. Below is a brief mention of some common quality methodologies found in biomanufacturing. Note – *not all quality systems adopted are mandated by law – some are voluntary!* We will explore why a company would take on additional quality systems beyond what is required by law!

- ✓ Current Good Manufacturing (CGMP) is a set of FDA-enforced manufacturing guidelines, which oversee the production of drugs. The goals of CGMP regulations are to ensure product quality, safety, and regulatory compliance.

- ✓ ISO9000 is a quality standard that has been developed to provide guidelines for improving quality management systems. Eight key principles are integrated into ISO9000 standards: customer-focused organization, leadership, the involvement of people, process approach, systems approach to management, continuous improvement, and factual approach to decision-making and mutually beneficial supplier relationships.

- ✓ Six Sigma is a methodological strategy that deals with product and system failures. To increase system reliability and reduce failure, companies utilize a rigorous process improvement methodology, Define-Measure-Analyze-Improve-Control, which encourages management decisions based on data.

- ✓ Lean production focuses on removing waste from production processes. Lean workers recognize the seven forms of waste: Producing defective parts, producing more parts than needed, excessive inventory, unnecessary activities, unnecessary movement of people, unnecessary transportation or handling of materials and people waiting.

Professional Quality Organizations

Let's Explore!

1. Look up the website for the American Society for Quality and give a brief description of the site.
2. How can you use this site to help you learn more about Quality principles?
3. What is ASQ and what do they do? In your own words, discuss their vision.

There are other prominent Quality professional organizations of note. One is RAPS (Regulatory Affairs Professionals Society). RAPS focuses on Regulatory Affairs training and certification as a non-lobbying nonprofit both nationally and worldwide. To learn more visit their website here: http://www.raps.org/. To keep on top of Regulatory issues in the news, visit their news trends page: http://www.raps.org/news-trends/

In summary

- ✓ The quality specification is defined by the customer.
- ✓ Specifications are used to help define a customer's needs.
- ✓ Quality assurance is the function that sets up the systems and methods for "assuring" the quality of the product.
- ✓ Quality Control is responsible for the testing or sampling in compliance with the specifications determined by QA.
- ✓ Every department in the company is responsible for quality

CHAPTER 2: INTRODUCTION TO QUALITY PRINCIPLES

OBJECTIVES

- ✓ Identify significant contributions to the field of quality from the following contributors: Deming, Juran, Crosby, Feigenbaum, and Taguchi.
- ✓ Discuss Total Quality Management and how it differs from other management styles.
- ✓ Apply the Plan-Do-Check-Act Cycle.
- ✓ Understand and apply Juran's 'fitness for use' definition of quality.
- ✓ Distinguish between inspection, audit, surveillance, prevention
- ✓ What is variation and how do specifications and tolerance limits relate to variation?
- ✓ What is nonconformance? How do you combat nonconformance? SQC versus SPC

HISTORY OF QUALITY

Quality philosophies have been around for as long as humankind has. Standards of quality were necessarily different then and, some might say, lower by our standards today. Where you and I might throw away a half-rotten apple, the nomadic cave dweller would likely judge the unspoiled half as a great dinner.

Areas of expertise in quality inevitably evolved alongside the division of labor into hunting and gathering, and this knowledge was passed down from generation to generation. It evolved further still as humankind began to settle into relatively permanent locations and start the practice of agriculture. Settlements grew into villages with full-fledged marketplaces where a buyer could come to inspect a producer's product and provide immediate feedback as to its quality. There was no middleman between buyer and seller. In fact, the consumer and producer usually lived in the same village. Hence, the producer had a personal stake in maintaining quality: his reputation. A buyer could quickly spread the news of a poor quality product by word of mouth.

The Effects of Growth on Commerce. As population growth transformed villages into towns and cities, and new routes and methods of transport opened up to expand trade into larger geographical regions. A producer and consumer living in the same village could rely on oral warranties and face-to-face meetings to resolve quality concerns; but what happened when the two lived many miles apart from each other?

Here we see the birth of the "intermediary" or wholesaler, and the idea of the written warranty. The wholesaler became a kind of communications liaison between buyer and seller in that he not only transported and sold products on behalf of the producer but also negotiated quality specifications between the two. In the case of material goods, for example, a buyer could specify requirements to a wholesaler who would report those conditions back to the manufacturer.

Naturally, conflicts arose in this area due to differing ideas between buyers and sellers when it came to issues of quality and quality testing. Hence, the concept of establishing standards of quality testing and inspection evolved out of necessity, which inevitably led to the standardization of measuring instruments and the need to calibrate them as well. A good example of this is the ancient Egyptian unit of measure known as the "cubit." The cubit was determined to be the length of the Pharaoh's forearm. Measuring sticks were made to match this length and subsequently used by every architect as a standard measuring tool.

Soon after that, the idea of the "Mark" or "Seal" was developed as a means of identifying and tracing the origins of a product. The seal gave buyers a modicum of assurance as to the quality of a product. This approach to quality assurance is with us even today. Meat and dairy products, for instance, come stamped as "USDA Approved." Likewise, the various electronic appliances we use every day are tested to meet such standards as the ANSI specification.

An Early Example of Quality Control. In ancient Rome, bridge engineers were required to stand under their finished product while the bridge was weight-tested by various types of traffic. Although this was a very harsh method of ensuring quality, it apparently worked given that many of those structures still stand to this day. What the Romans understand very well was the necessity of holding people accountable for quality products. As skillful as the Romans were, however, their philosophy of quality lacked an understanding of the need to set standards and specifications that did not change over time or at the whim of individual judgment. This was true not just of the Romans but most other cultures. It was not until the industrial revolution that we begin to see notions about quality mature towards the idea of controlling for consistency in the manufacturing process.

The Industrial Revolution. Efforts towards developing a means of mass production arose in the United States during the Civil War when the U.S. government contracted with Eli Whitney to manufacture 700 muskets with interchangeable parts. The hope was that, by setting standard specifications for each piece, the natural variations introduced by handcrafted production is reduced enough to allow failing parts to be replaced in the field. The central idea of mass-producing identical, interchangeable parts carried forward despite the fact that Whitney's attempt to solve the problem was a relative failure with only 14 muskets correctly assembled.

Most products continued to be crafted and inspected one at a time by individual artisans and craftspeople until Henry Ford revolutionized the manufacturing industry with the introduction of the assembly line. No longer was production the responsibility of one person. Instead, dozens of workers operated the assembly process, and the responsibility for quality assurance fell to supervisors. As growth continued, the average number of employees on an assembly line climbed into the hundreds, and quality became the responsibility of an entire inspection department. The increase in numbers beyond this point lead to the introduction of the statistical sampling in today's manufacturing environments.

The Effect of Culture on Quality: The Taylor Method. Changes in production methods were not the only factors affecting quality control. A growing need for skilled workers coincided with the influx of non-English speaking immigrants to the U.S. from 1860-1920. Differences in language, culture, and skills among these workers introduced new variables into quality control. Many of these immigrants had never seen nor worked on an assembly line, and language differences presented a clear challenge when it came time to train them.

A mechanical engineer by the name of Fredrick Taylor was the first to address this problem by automating each part of the manufacturing process into a series of repeatable steps these workers could learn and execute only by watching and then doing. In essence, he eliminated the need for any assembly line worker, English speaking or not, to do anything other than learning their steps by rote and perform them robotically. Issues of quality became the sole authority of management. Workers' feedback on such matters was often ignored and usually dismissed entirely. This polarized and often created an adversarial relationship between labor and management, which continues in many industries even to this day.

After World War II. Manufacturing industries across Europe and Asia (specifically Japan) were devastated in the aftermath of the Second World War. In those countries where the war was fought on their soil, entire factories were decimated. The American manufacturing industry, however, was unharmed and meant a huge surge in U.S. dominance in manufacturing as no other country had the capacity to fill the resultant worldwide shortage of goods. It also meant that producers of goods in the U.S. had the luxury of dictating product requirements and quality to the public rather than responding to the type of feedback that would otherwise inform a genuinely competitive marketplace.

It was not until foreign companies recovered and targeted this weakness in U.S. attitudes that U.S. businesses succumbed to paying better attention to customer needs. Where U.S. industries remained cavalier about product quality, overseas companies, particularly Japanese firms, solicited customer feedback and willingly responded to those needs and demands. They also developed management philosophies that respected the needs of labor. It was not long before these foreign companies began to outperform the U.S. in manufacturing. The steel industry in Japan, for example, thrived while in the U.S. many companies faced insolvency and were forced to lay off their workers.

Need for Quality in Today's Business Environment. By the 1980's, the U.S. manufacturing industry had lost so much ground that it was no longer considered the leader in the production of consumer goods. Nowhere was this fact clearer than in the automobile industry. Year after year, sales of domestic vehicles slipped as the Japanese and Koreans outpaced the U.S. in price, quality and customer satisfaction. Quite simply, these foreign manufacturers took their cue from the lessons that American businesses continued to ignore – the most important one being the necessity of making a commitment to quality and quality control. Quality plays the deciding role in a company's ability to mass-produce competitive products at a level of quality and at a price point that satisfies both the consumer's needs and company's profit margin.

To endure in today's global marketplace, companies focus understanding of the importance of quality into three major areas: marketing, profit, and liability.

- Marketing: The features or "bells and whistles" of a product might be highlighted. In many cases, however, the consumer is much more concerned with quality and will respond better when quality is used as a selling tool.
- Profit: To improve profits, many companies are focusing on improving not just the quality of the products themselves but also their manufacturing methods and training of employees on the production line.
- Liability: A company can be driven out of business by lawsuits and the resulting financial settlements. The best line of protection is to limit exposure in the first place, which can be achieved by allowing the Quality department to work closely with R&D, Manufacturing, Marketing, and Warranty Departments to identify and limit areas of potential liability.

QUALITY PIONEERS

Good quality management techniques are as numerous and varied as the types of biotechnology companies that use them. Most companies will lean towards a 'favored' quality philosophy, but few rely on just one. It is much better to draw from several schools thought. We will present some of the major contributors to the field of quality below. You are encouraged to research more on these pioneers interesting backgrounds!

Dr. Walter Shewhart (1891-1967) developed statistical methods that are applied to improve quality processes that provide both goods and services. While at Bell Laboratories, Dr. Shewhart was the first to encourage the use of statistics to identify, monitor and determine the source of variation found in repetitive processes. His work was to target and remove sources of variation.

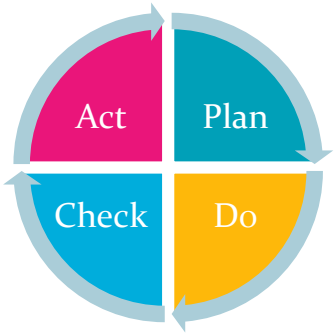
Dr. Shewhart recognized two sources of variation in a process; controlled variation and uncontrolled variation. In a controlled variation, the variation is present internal to the process, also referred to as common causes. In an uncontrolled variation, the variation comes from a source, which is external to the process, also known as assignable causes. Dr. Shewhart determined that once a process is under control, the process performance could be predicted. The most influential contribution of Dr. Shewhart is statistical process control charts. These charts provide a framework for monitoring the behavior of a process and provide feedback to help an organization improve the process.

Dr. W. Deming (1901-1993) was one of the preeminent figures in the quality control profession. Deming worked as a consultant to the U.S. War Department during World War II. After the war, he adapted the technique he had developed for quality improvement in the War Department to private industry. This method *centers on statistical controls on manufacturing processes and cooperation between management and labor*. Deming believed that the majority of quality problems were generated by management and created a philosophy to facilitate quality improvement in a company through better management.

Mass inspection of the product was replaced by statistical methods, extensive training of personnel, and two-way communication between the workers and management. Deming pushed for a cooperative atmosphere between the employees and management by increasing the employee's status through encouraging participation in solving problems and giving the training to facilitate this. *The W. Edwards Deming Award for Quality* is a national award presented annually in Japan to the company that has demonstrated the greatest quality improvement effort and to the individual who has been responsible for the most significant quality improvement.

PLAN-DO-CHECK-ACT CYCLE:

The Plan-Do-Act Cycle is a four-step process for quality improvement and is used as a model for improvement of a current project or when starting a new improvement project. The first step is to develop a plan to effect improvement. In the second step (do), a small-scale plan is carried out. In the third step (check), a study takes place to check if the plan was carried out. The last step (Act), an action is taken to effect change in the system if there are any disparities between the Plan and Do. At this step, you use what is learned to tackle new improvement projects, and the cycle continues. Again, this is a CYCLE for CONTINUOUS improvement.



The Plan-Do-Check-Act Cycle

The plan-do-check-act cycle is sometimes referred to as the Shewhart cycle; because Walter A. Shewhart discussed the concept in his book *"Statistical Methods from the Viewpoint of Quality Control,"* and is also referred to as the *Deming Cycle* because W. Edwards Deming introduced this concept in Japan.

Using your results/grade from your first homework grade, create your own Plan-Do-Check-Act Cycle for improving your studies on your Quality Assurance Homework Assignments.

THE JURAN TRILOGY

Dr. Joseph Juran (1904-2008) was one of the foremost experts in the area of quality. Juran believed that to achieve quality, you must start with organizational goals, policies, and vision. Converting organizational goals into results is accomplished through three managerial processes called the JURAN TRILOGY: Quality Planning, Quality Control, and Quality Improvement (The Juran Institute, 2016). To learn more about Juran, visit the Juran Institute. https://www.juran.com/

1. Quality Planning: *"Quality does not happen by accident, it must be planned."* Quality planning is the structured process of designing products and services to meet new goals and ensure that customer needs are met.

Quality Planning Steps:

1. Establish the project.
2. Identify the customers.
3. Discover the customer's needs.
4. Develop the product.
5. Develop the process.
6. Develop the controls and transfer to Operations.

2. Quality Control: Quality control is a universal managerial process for conducting operations to provide stability, to prevent adverse change and to "maintain the status quo." Quality control can also be described *as "a process for meeting the established goals by evaluating and comparing actual performance and planned performance, and taking action on the difference."*

The quality control process:

1. Choose control subject.
2. Establish Measurement.
3. Establish Standards of Performance.
4. Measure Actual Performance.
5. Compare to Standards (interpret the difference).
6. Take action on the difference.

3. Quality Improvement: *"All improvement takes place project by project."* Quality improvement is the process of creating breakthrough levels of performance by eliminating wastes and defects to reduce the cost of poor quality.

Steps to Quality Improvement:

1. Prove the need for improvement.
2. Identify the improvement projects.
3. Establish project improvement teams.
4. Provide the project teams with resources.

Juran's Fitness for Use. Quality begins with whom, how, and why customers will use a product; all improvement activities should be customer focused. Juran's fitness for use definition of quality means the product should be a good price, work well for the customer, be distributed efficiently from the producer to the customer, and be supported efficiently by the company. Juran's four components of product fitness:

- Quality of Design: A successful company conducts market research and creates satisfied customers by building their needs into the product design. The quality of design must also take into account the intended functions of the product and the type of conditions in which it will perform. Another consideration affecting the quality of design is cost. How much will it cost to make the product?
- Quality of Conformance: Does the manufacturing process adhere to specifications? Attention to conformance can be a vital tool and decrease the cost of manufacturing as it reduces the likelihood of these types of catastrophic failures.
- Availability: In the customer's view, availability and reliability are often synonymous. For example, if a customer attempts to order a laboratory instrument from a company he has ordered from in the past, only to find out that the product is out-of-stock and will be on back-order for a month, his level of customer satisfaction goes down. Quality, as it relates to availability, can be a matter of maintaining inventory and ensuring availability as in the above example, and it can also be an issue of speedy shipping and have a good distribution infrastructure. Some other examples of accessibility as it relates to quality include reliability, maintainability, and customer service.
- Field Service: Field service personnel are, typically, the technicians who deliver, install and set up products, providing training to the customer on proper use and maintenance.

Philip Crosby (1926-2001) was an American-born author and business executive, noted for his contributions to the management of "quality crises." He is credited with effecting a 30% reduction in costs incurred through scrap waste when he served as the lead quality control manager for the Pershing Missile program. Later in his career, when the U.S. manufacturing industry faced a quality crisis and stiff competition from the Japanese, he responded with the creation of the DIRFT principle. Short for "doing it right the first time."

Crosby's DIRFT philosophy on quality:

1. Quality means conformance to requirements.
2. Quality systems should focus on prevention of nonconformance.
3. The performance target should be "zero defects."
4. The cost of nonconformance should be the standard by which quality is measured.

Ultimately, Crosby's guiding principle was that robust quality assurance systems pay for themselves in the end and are more than worth whatever initial costs a company must absorb to establish such a system. Additional insight into his philosophies can be found in his first published book; Quality is Free.

Dr. Kaoru Ishikawa (1915-1989) is best known for his creation of the "Fishbone" or "cause and effect diagram." This type of chart is used in an evaluation of industrial processes. The Fishbone diagram is not his only innovation in the area of quality, however. He also introduced the idea of "quality circles." A quality circle is a volunteer group of individuals within a company who are trained to analyze and solve work-related problems, sharing their insights with upper management. This quality circle theory was a direct shoot-off from Deming's Plan-Do-Act-Check cycle. It should be noted that Dr. Ishikawa was intimately familiar with Deming's work and many of his contributions to quality philosophy arose as a direct result of his lifelong work in synthesizing and expanding Deming's ideas into Japanese corporate culture.

Dr. Genichi Taguchi (1924-2012) was a Japanese engineer and statistician known for his development of the 'Taguchi Methods', which represent a type of statistical methodology for improving quality in the manufacturing process. Many industrial statisticians in the U.S. are coming to accept his ideas after years of resistance. There are two key philosophies from the Taguchi Method that stand out as representative of his views on quality. The first is that poor quality represents a loss to society as a whole, not just the individual consumer. The nature of this loss can be calculated using any number of loss functions to derive a real number cost from a variable (the Taguchi method uses the "mean-squared-error" approach).

The second philosophy to consider is what Taguchi referred to as "offline quality control." Offline quality control just means that processes and products should be designed to be robust within the production environment itself so that factors outside of the design engineer's control had little to no effect on quality. Also these contributions to modern thoughts on quality, Taguchi also made several innovations to the statistical design of experiments. His concepts of experimental design, loss, and variation have made an impact in many industries beyond manufacturing!

FEIGENBAUM - TQM

Dr. Armand Vallin Feigenbaum (1922-2014) was an American-born quality expert. He devised the concept of Total Quality Control, later coined as Total Quality Management (TQM) https://youtu.be/-W2aycTEK1Q (Feigenbaum Foundation, 2016). TQM is an extensive, company-wide, quality improvement program. It gets everyone involved in developing an agreed-on company-wide and plant-wide work structure documented ineffective, integrated technical and managerial procedures. Integration provides coordination to the actions of the workforce, machines, and information of the company in the most practical ways, ensuring customer quality satisfaction and economic costs of quality. To learn more about Feigenbaum, visit the Feigenbaum Foundation. http://www.feigenbaumfoundation.org/

Often a company quality control department only focuses on production. However, Feigenbaum realized that the customer might have a problem not only with the product but also with the call center, shipping or records. TQM is a consumer-based improvement system, and all of the workers need to participate and educated. He identified 10 product and service conditions that must be met or considered to satisfy customer requirements. The aim of these requirements is that quality establishes the proper balance between the cost of the product or service, and the 'customer value' it renders (including safety).

Feigenbaum's 10 Product and Service Considerations:

1. Specification of dimensions and operating characteristics.
2. Life and reliability objectives.
3. Safety requirements.
4. Relevant standards.
5. Engineering, manufacturing, and quality costs.
6. Production conditions under which the product is manufactured.
7. Field installation, maintenance, and service objectives.
8. Energy utilization and material conservation factors.
9. Environmental and other side effects considerations.
10. The cost of customer operation and use, and product service.

Today quality involves a total company commitment to quality. The TQM approach states that every employee in the business is responsible for quality. Note that this is distinct from the old model of an adversarial relationship between labor and management and closer to the model of labor-management cooperation. *"Total Quality Management (TQM) is a management approach that places emphasis on continuous process and system improvement as a means of achieving customer satisfaction to ensure long-term company success."* (Summers, 2010)

TQM is not a temporary fix or used for short-term problem solving. A long-term, deeply committed management style is dedicated to the improvement of the process on an unwavering commitment to meeting the customers' needs. Since their needs are continually changing, TQM must also be amenable to change. Later assignments will explore TQM as well as other management styles to help meet customer needs.

The TQM philosophy influencing corporate culture:

- ✓ leadership
- ✓ information and analysis
- ✓ strategic quality planning
- ✓ human resource development and management
- ✓ management of process quality
- ✓ quality and operational results
- ✓ customer focus and satisfaction

Let's Explore!

Learn about Total Quality Management (TQM) at this website. http://managementhelp.org/quality/total-quality-management.htm

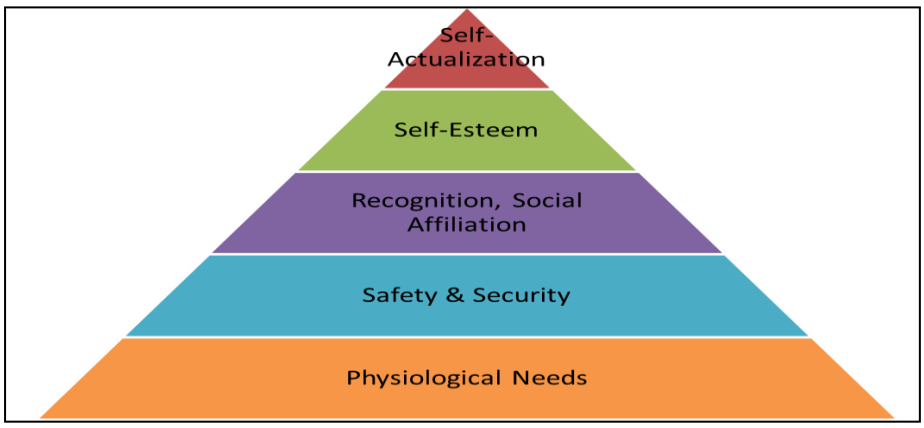
a. In your own words, describe TQM.
b. It can be difficult to get employees on board with a new management style. What are some things you would recommend to help transition employees in a positive way to this management style?

How to Change Culture in a Company

Changing culture within a company can be a long, daunting process. Even in the best of circumstances, the change will not happen overnight. Quality professionals are limited in their ability to alter the culture of a manufacturing organization. For real change to occur everyone in the organization must be motivated to change. A successful company takes care of its employees' basic needs by cultivating a culture of respect, fairness, and rewards for a job well done. These key ingredients are powerful motivators that inspire employees to work hard and conscientiously for the company.

Maslow's Hierarchy of Needs is a psychology approach that was proposed by Abraham Maslow and first expressed in his paper *"A Theory of Human Motivation,"* published in 1943 and was more fully formulated in 1954 in his book *"Motivation and Personality."* Very simply put, the further up the pyramid an employee can go, the more connected that employee feels to that company. Although Maslow himself never used a pyramid to describe this theory, it is still a good way to pictorially represent the message.

To affect change management must understand where employees are in Maslow's hierarchy, identify their needs and convince all individuals they must become involved in the system to improve it. This change must be a priority. Remember that people's perceptions are as important as their reality, and what people value differs from person to person. Learn more here about Maslow's Extended Hierarchy of Needs motivational theory. https://youtu.be/yM8SwZkvCIY



Maslow's Hierarchy of Needs

ESTABLISHING QUALITY CONTROL – THE ESSENTIALS

Every company develops a routine way of doing things, but what happens when the way they are doing things no longer works for reasons out of their control? What if the market changes? What happens when the customer needs change? What about the needs of their workforce? How an organization adapts to a rapidly changing market and customer base is crucial to its survival.

Process & Process Improvement: A process collects inputs and provides value-added activities on those inputs to create an output. We do this every day without even realizing it. For example, we want to repaint our bedroom – what color to choose, the type of paint to use, the rollers, and who will perform the job? In our everyday life, most processes develop over time without any thought to their effectiveness, and the same happens with businesses. Companies must identify the processes and determine their effectiveness. Ineffectual or wasteful processes must be removed or changed for a business to stay successful.

Variation: Variation is a natural part of any process. Scientists have now discovered that even identical twins have small differences in their genetic makeup. Therefore, it goes with the production of a product. There are rarely two products exactly alike; there is always some small amount of variation. Companies interested in providing quality products use quality techniques to study the variation present in their process. When they discover the source of the variation, they can move toward a more consistently produced, higher quality product.

Specifications: Specifications are substantive requirements provided by the customer. There are many forms specifications can take depending on the product produced and its target customer.
Specifications are descriptions that define and characterize properties that a product must possess for its intended use. There are specifications for both raw materials and products. As quoted from an FDA document (*Guideline on General Principles of Process Validation,* Food and Drug Administration, 1987): *"The desired product should be carefully defined regarding its characteristics, such as physical, chemical, electrical and performance characteristics...It is important to translate the product characteristics into specifications as a basis for description and control of the product."*

The table below provides an example of the broad range of specifications for the same chemical, in this case, sodium chloride. Notice the purity differences, the physical requirements, and additives – these specifications are based on intended use. ***These specifications illustrate several important points:***

1. Properties that are necessary for that product based on its intended purpose.
2. The specifications for the same property may vary depending on intended use.
3. Specifications always are associated with analytical methods.

Specification	road salt	table salt	Analytical grade salt
Chemical purity	minimum 95%	minimum 97%	minimum 99%
Color	clear to white, yellow, red, black	clear to white	clear to white
Maximum allowed contaminants	Not specified	As 0.5 ppm Cu 2.0 ppm Pb 2.0 ppm Cd 0.5 ppm Hg 0.10 ppm	Al < 0.0005% As < 0.0001% Ba < 0.0005% Ca < 0.002% Cu < 0.0005%
Physical requirements	90% of crystals between 2.36mm and 12.5 mm	90% of crystals between 0.3 mm and 1.4 mm	95% of crystals between 0.18mm and 0.3 mm
Allowed additives	Anti-caking agents of 5-100 ppm, Sodium Ferrocyanide, Ferric Ferrocyanide	coating agents, hydrophobic agents	not allowed
Moisture	2-3%	< 3 %	not specified

It is important, for example, that road salt is not used for cake salt. Table salt is stored in containers that are open to the air, so it is important to include agents that absorb moisture from the air instead of the salt. These hygroscopic agents must be excluded from the analytical grade salt. Additionally, analysis of the analytical grade salt shows that it is free of contaminating metals as it may be used in techniques that are ruined by metal contamination or in techniques where the instrumentation would detect the metals, thereby interfering with the intended measurements. Sodium chloride could be a raw material for a biomanufacturing company. It is important that specifications for it are determined, documented, and a contract between the supplier and the company based on those specifications is established.

The term "establishing specifications" means:

- ✓ Defining the characteristics of the product, material, or process.
- ✓ Documenting those specifications.
- ✓ Ensuring that the specifications are met.

It is very important to establish specifications during the development of the product, for the product itself, all raw materials and the process as part of the application to the FDA. This is not a simple task. It requires knowledge of how the product, materials, or process will be used, the properties that will make it suitable for that use, and the ranges that are allowable. If the range for a specification is too stringent, then adequate materials might be rejected. On the other hand, if the range of values for the specifications is too broad, then the quality of the product is not protected. Because the setting of specifications is both a critical component of a quality program and a challenging task, the FDA scrutinizes specifications for products it regulates. *The FDA will not accept specifications if they are not complete, if they are unsuitable for the product, if their range is too broad, if they are unsubstantiated by testing, or if suitable analytical methods to test them are not available.*

Tolerance limits: Tolerance Limits are the permissible changes in the specification. A product's process is considered to be 'under control' when the specification is met within the tolerance limits provided by the customer.

Out of Specification. *If samples do not satisfy specifications, then they are out-of-specification (OOS).* If this occurs, operators may follow a procedure to correct the problem, or they may initiate an investigation. The FDA recognizes that from time to time a batch of a product will be found not to meet all product release criteria. However, the FDA expects that the batch is not just thrown away but that the company must know why the batch did not meet requirements and determine if the "failure" is an isolated, explainable incident, or an indication of a significant problem associated with the manufacturing and control of a drug. This "explanation" must be in writing, supported by evidence, and reviewed by management and approved by at least QA. OOS laboratory data may be the result of lab error, non-process

error or operator mistake (i.e. used wrong raw material or ingredient did not correctly follow manufacturing instructions) or process problem (i.e. equipment malfunction or process too variable or fundamentally flawed).

Productivity: Productivity may be defined as working effectively while best utilizing the available resources. Productivity is a little different from quality, which just focuses on effectiveness – achieving goals while meeting customer needs. Improvements in productivity and quality come from managing the work activity regarding processes. Measuring effectiveness of processes, helps identify areas of increased productivity.

Processes. Processes make products. ISO 9000 defines a process as "*a set of interrelated resources and activities which transform inputs into outputs.*" **Inputs** are raw materials. **Outputs** are products or intermediates that led to products. **Resources** include personnel, facilities, equipment, and procedures to make a product or intermediate. To obtain a quality product, it is essential that processes be carefully designed and developed by the R&D unit. Production operators in a biotechnology company participate in setting up, monitoring, and controlling the operations.

The design of a process begins during the R & D phase and is defined as the product enters production. Every process is designed so that all inputs are efficiently converted into the desired product. An important aspect of developing a process is to find ways to monitor and control it to prevent problems and to quickly adjust the process if a problem occurs. To do this one has to completely understand the process and the factors that can affect it and know what needs to be monitored or tested during the process (i.e. in-process testing) to prevent problems. For example, what is the pH range for this process and what will happen to the cells if this range is exceeded?

These points in the process are known as the "***critical points***" or the "***control points.***" Monitoring and controlling a process may occur in a variety of ways. For example, temperature and pH probes may be inserted into the fermenter. If the temperature or pH exceeds certain limits, then operators can perform corrective actions. Specifications are established for the testing and the corrective measures.

INSPECTION, AUDIT & SURVEILLANCE

Inspection, audit, and surveillance are three tasks conducted in the quality effort that may cause some confusion to a newcomer in quality. Similar in some ways, and unique in others, each has a different purpose.

Inspection: various Inspections are best used to gather data for a proactive approach to problem solving. *Not only should the inspection be used to identify a nonconforming product, but it should also collect the data needed to determine the root-cause of the problem and to find and monitor the remedy.* Inspection may involve:

- Receiving inspection: Ensures items received from vendors meet requirements of the purchase order.
- Source inspection: Review the vendor facilities to make sure they conform to quality standards.
- In-process inspection: Ensures quality during fabrication or assembly.
- Final inspection: Review plan-and-process sheets to verify all steps were correctly performed, quality of materials were used, final tests were coordinated with the customer, inspect spare parts, and check shipping containers to assure safe delivery of a product.

Unique processes inspections such as metrology (maintain the accuracy of tools gauges) or nondestructive examination. Examples of this type of analysis are looking for variations in color such as in a final product (i.e. an allergy kit contains colored solutions instead of clear solutions).

Audit: An Audit is an inspection of an organization's adherence to the established quality standards. In a small start-up company, it may be possible for one person to perform or at least supervise all of the aspects necessary for the production and testing of a product. As the operation grows, however, it is no longer likely that a single individual is knowledgeable in all functions or confident of the level of quality employed during all operations. Therefore, systems must be set up for the accumulation of data and for the review of that data. In addition, the systems themselves must be examined, or audited, to determine that they are still operating as originally planned.

A company can do an internal audit (by people from the company itself) or hire an external auditor (people from outside the company) to make sure that they are following established quality standards. In some cases, an external agency, such as the Food and Drug and Administration (FDA), could audit a biotechnology company to ensure that they are following current good manufacturing practices (CGMPs).

The quality audit should be designed to answer three basic questions about the organization being audited:

1. Quality System: Does the organization have a quality system? This is usually evidenced by a quality manual, operating manual, or quality procedures.
2. Adherence: Is the quality system being followed? An audit is conducted to determine whether the procedures are adhered to on an ongoing, consistent basis.
3. Effectiveness: Is the system effective? Are the results of following the procedures consistent and positive?

The auditor does not carry the authority to make corrections in the procedures, so the results of the audit are given to upper-level management for further action. However, the auditor will follow up on findings and recommendations to ensure the recommended changes have been implemented. In the case of a regulated industry, the process and frequency of a quality audit may be defined by the regulating agency. In this case, the audit program of the industry is often subject to inspection by the regulatory agency. For example, an industry regulated by the U.S. Food and Drug Administration (FDA) must provide access to an FDA inspector to its audit procedures. The manufacturer may be asked to provide evidence that its audit program is functioning, is well-documented, and is instituting corrective measures when appropriate. A certification by an outside auditor or access to an internal audit log (or history) may be used to demonstrate that the system is in compliance.

Surveillance: Surveillance is an alternate inspection process that uses some of the techniques of both the audit and inspection functions, although less precise than either of the two. Most commonly, surveillance is an objective evaluation to determine how well the quality procedures are being followed in day-to-day production, along with determining how well the procedures, when followed, maintain the quality of the product. Surveillance answers the questions,

- ✓ Is the process of performing as planned?
- ✓ Is the product of acceptable quality?
- ✓ Have the recommendations of the audit been incorporated?

VALIDATION OF PROCESSES & EQUIPMENT

- ***Calibration*** is a process that compares a known (the "standard" device) against an unknown (the target device in question). During the calibration process, the offset between these two devices is quantified, and the target device is adjusted back into tolerance (if possible). A calibration report usually contains both "as found" and "as left" data. When a micropipette is determined to be out of calibration, it is typically sent to the manufacturer for recalibration.

- ***Verification*** is simply the process of "verifying" that a device is within tolerance (within an acceptable range). Verification usually results in "as found" data. If the device is not within tolerance, it is sent for recalibration.

- ***Validation*** is a detailed process of confirming that the instrument is installed correctly, that it is operating efficiently, and that it is performing without error. Validation in the pharmaceutical industry emerged from problems in the 1960s and 1970s and went hand-in-hand with the QA/QC philosophy that quality is built into the product not tested into the product. The FDA states that quality, safety, and effectiveness are designed and built into the product.

Each step in the production process must be controlled to ensure that the finished product meets all quality and design specifications. The actual requirement for process validation comes from the text of the GMPs, Section 211.100 which states that ***"there shall be written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess."*** **(fda.gov)**

BIOMANUFACTURING VALIDATION

There are three main areas of validation for a biomanufacturing facility. You must validate your process, your equipment, and your methods. The planning of validation occurs throughout the development of the product. The actual validation process is usually performed before large-scale production and marketing of a product begin. Revalidation is required whenever there are changes in raw materials, equipment, processes, or packaging that could affect the performance of the product.

Validation is important both in "traditional" pharmaceutical manufacturing and in the production of medical products using biotechnology methods. FDA's "Guideline on General Principles of Process Validation" (May 1987) is a general guide that applies to most manufacturing situations. There are also specific guidelines for the biotechnology industry, which is found at the FDA website. Validation is a major undertaking that is expensive, time-consuming and requires extensive planning and knowledge of the system being validated. The advantage to validation is that it helps to assure consistent product quality, greater customer satisfaction, and fewer costly product recalls.

I. PROCESS VALIDATION. Process validation *is the method by which companies demonstrate that their activities, procedures, and processes consistently produce a quality result***.** For example, process validation of a sterilization process might involve extensive testing of the effectiveness of the process under varying conditions, when different materials are sterilized, with different operators, and with various contaminants to make sure that the technique can "clear" the material of the contaminant. During this testing, the effectiveness of contaminant removal would be measured, the temperature and pressure at all locations in the sterilizer would be measured and documented, and any potential difficulties would be identified and recorded. Validation demonstrates *that the process is effective*. Validation and final product testing are recognized as two separate, complementary, and necessary parts of ensuring quality.

Read more about Process Validation FDA Guidelines:
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf

Discuss the three stages of process validation.

What are the Guidances on documentation?

II. EQUIPMENT VALIDATION. Processes usually involve equipment. For a process to proceed correctly, the equipment must be of high quality, must be properly installed, regularly maintained, and properly operated. Equipment must, therefore, be validated or qualified to ensure that it will function reliably under all the conditions that may occur during production. Equipment qualification may be and performed separately from process validation, but it is also a requirement for process validation. Equipment Validation is a detailed process of confirming that an instrument is installed correctly, that it is operating efficiently, and that it is performing without error. Equipment Validation is divided into three parts:

- **Installation Qualification (IQ).** First, the equipment item is checked to be sure that it meets its design and purchase specifications and is correctly installed; this is called installation qualification. Installation qualification includes, for example, checking that instruction manuals, schematic diagrams, and spare parts lists are present; checking that all components of the device are installed; checking that the materials used in construction were those specified; and making sure that fittings, attachments, cables, plumbing, and wiring are properly connected. IQ is documented proof that the building, wiring, installation and calibration of equipment, utilities, SOPs, spare parts and specifications meet the design intention.

- **Operational Qualification (OQ).** After installation, the equipment can be tested to verify that it performs within acceptable limits. For example, an autoclave might be tested to see that it reaches the proper temperature, plus or minus certain limits, in a set period; that it reaches the correct pressure, plus or minus certain limits, etc. The penetration of steam to all parts of the chamber, the pressure achieved at various settings, and so forth, would all be tested in the context of the operational qualification of an autoclave. OQ is documented proof that the equipment performs as specified.

- **Performance Qualification (PQ).** Once all measuring instruments are calibrated, and all equipment is validated, process validation (or qualification) can be performed. The validation of the process will involve assessing the process under all the conditions that can be expected to occur during production, including running the process with all of the raw materials that will be used and performing all the involved activities according to their SOPs. Testing includes checking the process endpoint(s) under these conditions and establishing that the process consistently meets its specifications. PQ is documented proof the equipment or systems operate as intended under challenge conditions.

  PQ also involves challenging the system with unusual circumstances. FDA speaks of the "worst case" situation(s) that might be encountered during production. For example, a sterilization process might be challenged by placing scores of an especially heat-resistant bacterium in the corner of the autoclave known to be least accessible to steam. The effectiveness of bacterial killing under these "worst case" conditions must meet the specifications for the process.

III. METHOD VALIDATION. Refers to the testing of the raw materials, the intermediates, and the product.

Unplanned Occurrences. After these validation activities have been performed, the collected data is analyzed as described in the validation protocol and a report is prepared. *Successful validation demonstrates that a process is effective and reliable.* With careful validation design, planning and implementation problems are easily avoided.

Even in the most carefully designed facilities, unplanned occurrences happen. These unexpected events are called ***deviations***, and every company must be prepared to deal with them. Typically, the validation plan will have a form for documenting the deviation. The supervisor and the quality department will review the deviation to determine the plan of action to correct the deviation.

Nonconformance. When a process, product or raw material is out of specification, it is called a nonconformance. Inspections, audits, and surveillance will occasionally uncover nonconformance or defects. Nonconformance problems are placed in one of three categories based on the product defect: critical, major, and minor.

- Critical Defect: A defect that knowledge and experience indicate is likely to result in unsafe conditions for people utilizing, maintaining, or depending on the product. When Firestone found that their tires could blow out suddenly, causing accidents, this was a critical defect that triggered a massive recall effort.
- Major Defect: A major defect is a non-critical error that is likely to result in either product failure (non-life-threatening) or a significant, material reduction in the usability of the product for its intended purpose. If the plastic used in a blender lid, for example, bends in hot water, so it no longer fits the blender and liquids splatter everywhere, the blender lid would be said to have a major defect.
- Minor defect: "A defect that is not likely to reduce materially the usability of the unit of product for its intended purpose, or is a departure from established standards having little bearing on the effective use or operation of the unit." (Summers, 2010). For example, plastic drinking glasses that turn cloudy in the dishwasher, but are structurally sound, is a case of a minor defect.

It must be stressed that these three categories are not the only possible classifications and a company may define their classes of defects or break these standards down into types of even finer detail. Still, it is important that an employee can determine the impact of a defect and classify it appropriately so that the correct level of response is taken.

Read the following news article about a medical device recall: http://www.massdevice.com/deaths-prompt-abbott-recall-thoratec-heartmate-ii-controllers/

a. What type of non-conformance was this? (Critical, major, minor).
b. What part of the process do you think failed at catching this manufacturing error? (Inspection, audit, surveillance) Why?

Nonconformance Prevention. Statistical quality control (SQC) is the use of statistical methods to solve problems. Data on the product is collected, analyzed and used to solve product quality problems such as monitoring and control in the variation of the product. Also, statistics can also be applied to analyzing process methods to prevent defects, called statistical process control (SPC). SPC is particularly important in identifying activities that may result in defects and product nonconformance. It's important to note that the use of statistical analysis is essential in moving away from inspecting quality into a completed product and toward making process improvements to manufacturing quality into the product. Hence, the responsibility of quality passes from inspectors to manufacturing design personnel.

Statistical Process Control aids companies in achieving critical goals

- ✓ Consistently manufacture products that meet customer quality expectations.
- ✓ Reduce variability in product quality within and between manufacturing runs.
- ✓ Improve processes by identifying inefficiencies.
- ✓ Minimize production costs.
- ✓ Be solution-oriented and implement changes based on scientific analysis of problems.
- ✓ Assist with problem-solving process.
- ✓ Increase profits & productivity.

Changing Control Procedures. Deviations or OOS may not be a "negative" but a "positive." It is possible that change will result in improvement, but how is this change incorporated? In a highly regulated process, changes must be taken on conservatively and require the close collaboration of production personnel with quality assurance personnel. All changes must be carefully considered and thoroughly documented. A small change in one aspect of production may have an unpredicted change in another aspect of production or the quality of the final product. Rigorous testing must precede any changes that are instituted.

General Guidelines for change control procedures

1. Review and approval of the (proposed) change by Manufacturing, Materials, Management, Engineering, Regulatory Affairs, QC, and QA.
2. Verification of completion of required studies, reports, etc., supporting the change.
3. Proper documentation of all events surrounding the change.
4. A change control file that includes documentation of approvals, a history of change for each official document, and records and data to support the change.

A change in control procedures works best when it is planned and well thought out. One should ask how the change will affect process efficiency, worker safety, ease of equipment operation and product quality to name a few. If a problem arises, the personnel should have the training and the autonomy to do what they deem necessary at the time to prevent significant equipment damage, product loss or worker injury. Ideally, there is a plan that deals with such emergencies. This should be followed by a change control meeting as soon as possible to discuss and review the incident and follow the regular change control procedure from that point onward. Also, the company should document all activities done during the "emergency" period.

THE FUTURE OF QUALITY

The Buddhist philosophy that "Nothing is Permanent" is quite apropos when addressing Quality. Quality systems and methodologies continue to evolve and embrace change along with the pace of new technology products. It is important to remember that the customer affects the future of quality. This is a new, savvy generation demanding value and satisfaction. For organizations to create value, they will need the clarity of the customer's point of view. Quality systems put in place which is internal to the company will need to be adaptable and sustainable while attempting to eliminate waste. Competition is the driving force that encourages companies to seek ways to get the competitive edge.

SUMMARY

- ✓ To remain competitive, companies understand the importance of quality
- ✓ Many quality pioneers have contributed significantly to the field of quality; Shewhart, Deming, Juran, Feigenbaum to name a few
- ✓ Keeping processes in control is an important aspect of quality in a company
- ✓ Every process has variation – clear specifications, and tolerance limits are essential parameters when controlling these variations
- ✓ Inspections are close examinations of products and processes, audits & surveillance determine the adherence to a quality system
- ✓ Inspections, audits, and surveillance occasionally uncover defects; critical, major or minor
- ✓ There are three main areas of validation for a biomanufacturing facility; process validation, equipment validation & method validation

CHAPTER 3: QUALITY MANAGEMENT SYSTEMS

Objectives:
- ✓ Define a Quality Management System and outline its importance in producing a quality product.
- ✓ Discover various quality systems – both voluntary and mandatory
- ✓ Understand what ISO is and how it helps a company with quality. Identify different ISO standards
- ✓ Learn the basics of quality management; TQM, continuous improvement, Six Sigma, 5S, Lean, and ISO.
- ✓ Explore how a company earns ISO certification and CGMP certification. Understand who audits/enforces either of these QMS.
- ✓ Understand the motivation a company has to follow a QMS if they are not required to have one by law.

QUALITY SYSTEMS IN THE WORKPLACE

"A Quality System is the organizational structure, responsibilities, procedures, processes, and resources that together ensure the quality of a product or service." (Summers, 2010). The goal of all quality management systems is to encourage companies to: "...say what you are going to do, do what you say, be able to prove it and then improve it..." To meet the needs of the company, its customers, and regulatory body, a quality management system needs to be, accountable, dynamic and efficient.

It is important to note here; not all quality management systems are the same. *The type of system in any given company will depend on the size of the business, the nature of the firm, and the product they are selling.* In cases when a company is producing a federally regulated product, the company must follow Current Good Manufacturing Practices (CGMP) governed by the FDA. Other quality systems, such as the ISO9000 system, and 5S system are voluntary and assist a company with its business and production processes to achieve increased competitiveness and customer satisfaction.

In this chapter, you will be introduced to a few of the most prominent and influential quality management systems found in bioscience companies both regionally and nationally.

I. QUALITY SYSTEMS IN RESEARCH LABS

Academic research labs are usually self and peer-monitored in their quality systems. Government oversight is rare because these labs are not producing any product for public consumption. Instead, *academic labs focus on the pursuit of knowledge.* Furthermore, quality procedures in the university setting are based on following the empirically established, time-tested methods of *"good science."* In this regard, a certain level of quality is inherent in academic research. Results are judged through peer-reviewed publications and grant funding. The poor quality research will be rejected by the scientific community (peer-review publication), and unsuccessful nonproducing projects fail to gain funding or will lose funding.

Research Labs Associated with industry. These labs adhere to the regulations and standards related to the particular product they are researching. The research department of a pharmaceutical company, must follow the guidelines set out by the FDA and frequently submit to FDA inspections of their process and records which may include research laboratory notebooks, and research & development reports. Companies not regulated by the FDA may choose to implement a voluntary quality system such as ISO9000, 5S, or Six Sigma.

II. QUALITY SYSTEMS IN COMPANIES WHICH ARE REGULATED

The goal of government regulation is to protect public health. Any company producing drugs or medical devices will be governed by the FDA. Serious injury and even death can result from product contamination, deviation, failure, and errors in manufacturing and packaging. These types of events may be reduced or avoided altogether, when a company follows federally mandated quality guidelines, known as *Current Good Manufacturing Practices (CGMPs).*

These guidelines for product manufacturing and testing represent a formal quality system that describes the general principles that must be observed during manufacturing. It is the company's responsibility to ensure GMP compliance and to do so efficiently and effectively. To this end, regulations are relatively flexible. It is up to the manufacturer to establish design procedures, processing methods, and testing procedures. This flexibility gives companies room to experiment and innovate. Additionally, it should be noted that CGMPs represent only the currently accepted minimum standards for manufacturing, testing and packaging drugs and medical devices. Most companies go above and beyond minimum guidelines to assure a customer a high-quality product. They frequently employ multiple quality systems, including voluntary ones, which provides the consumer peace of mind and a level of trust in the safety of the product.

GMP guidelines follow a few basic principles:

1. Define, control and validate all critical manufacturing processes.
2. Changes to the manufacturing process must be evaluated and approved.
3. Instructions and procedures must be clearly written and easy to understand.
4. Production operators must receive thorough training on all processes and documentation of processes.
5. The company must maintain accurate records demonstrating their adherence to guidelines and regulations. Any deviations in product quality or quantity must be documented and investigated.
6. Records must be comprehensive, complete and easily accessible.
7. A recall system is in place so that any batch of drug may be easily recalled
8. The company responds to complaints, quality defects are investigated, and appropriate measures are taken to prevent future defects.

Let's Explore!

Explore the nutraceuticals company NuLab's website. http://www.nulabinc.com Watch the video on CGMP quality procedures: https://www.youtube.com/watch?v=kvICQiMFVi4 & https://www.youtube.com/watch?v=oRsZihZa4CQ
In what ways has NuLabs incorporated quality principles into their manufacturing facility?

Good Laboratory Practices (GLPs). In 1975, FDA inspection of several pharmaceutical testing laboratories revealed poorly designed and carelessly executed experiments on animals, inaccurate record keeping, poorly maintained animal facilities and a variety of other problems. These deficiencies led the FDA to institute the ***Good Laboratory Practices (GLP) regulations to govern animal studies of pharmaceutical products.*** GLPs require that testing laboratories follow written protocols, have adequate facilities, provide proper animal care, record data accurately, and conduct valid toxicity tests. *GLPs regulate all non-clinical safety studies that support investigative new drugs and new drug applications, biologics that are drugs, veterinary drugs, and some food additives.*

GLP laboratories are organized in a particular manner in seven general areas:

1. Organization and personnel (study director, quality assurance unit)
2. Testing facility (there are specific requirements for animal care)
3. Testing facility operation (each laboratory must base its functioning on Standard Operating Procedures (SOPs)
4. Test and control article characterization
5. The protocol and the conduct of the nonclinical laboratory study (a document, a plan, which indicates objectives and methods for conduct of the study)
6. Records and reporting (periodic audits and final report)
7. Equipment design (equipment must be appropriately designed and well maintained).

Good clinical practice (GCP), for hospital & clinicians clinical studies on new drugs in humans; regulations meant to ensure the quality of data submitted to the FDA on a new pharmaceutical to be marketed has been properly conceived and tested. These regulations also protect the welfare of human volunteers in clinical trials:

1. To protect volunteers participating in a clinical study, each participant must be informed about the study and treatment they are to receive so they can make an informed decision whether to participate.
2. To protect the rights and welfare of clinical subjects, the FDA requires that clinical trials be reviewed by a committee independent of the study sponsor called an ***Institutional Review Board (IRB).***
3. Another regulation defines the responsibilities of the trial sponsors and investigators during the conduct of a trial.
4. The FDA ***"Guideline for the Monitoring of Clinical Investigations"*** also explains the monitoring needed during a clinical trial, and how to document the process.

Enforcement. *The U.S. Food and Drug Administration (US FDA) enforces Good Manufacturing Processes under Section 501(B) of the 1938 Food, Drug and Cosmetic Act (21USC351).* Inspections are sometimes scheduled, but may also occur unannounced as long as they are conducted at a "reasonable time" as outlined in Section 704(A) of the FD&C Act (21USC374). Any time the company is open for business is the accepted definition of a "reasonable time." It is interesting to note that a product may be considered "adulterated" if the manufacturer failed to produce it by industry standards, even if the manufacturer did not violate any specific regulatory requirement. More on FDA enforcement in a later chapter!

III. QUALITY SYSTEMS IN COMPANIES WITH VOLUNTARY STANDARDS

Not all biotechnology companies produce regulated products. It makes good business sense for companies to impose some form of established quality system. They may choose to follow CGMPs or certain federal guidelines – but what most of these companies do is voluntarily adopt quality systems that are not government regulated.

International Organization for Standardization (ISO). One of the most prominent international quality systems is ISO. ISO is a quality system that can be applied to a wide-range of products. Participation is voluntary, and oversight is conducted through outside auditors paid for by the participating company. ISO standards can apply to more than just product design and specifications. There are also standards that outline things such as design methods and production processes based on currently accepted 'good practices.' The ISO system is so well-known and respected that the majority of companies who *can* voluntarily follow it *do* follow it. Below we will dive into a more in-depth discussion of the ISO system and how it applies in bioscience and biotechnology companies. *The mission of the ISO is: "to facilitate the international coordination and unification of industrial standards."*
(www.iso.org)

Let's Explore!

Visit the ISO website: http://www.iso.org/iso/home.html and learn about The International Organization of Standards.

a. What is ISO?

b. Who is responsible for the ISO 9000 quality standards?

c. What's new this year for ISO standards (hint: read their news!)

The need for a global standard arose because of the uneven progress of industrial development throughout the world. As manufacturing technology spread, many countries develop their own standards. Different processes and even different methods of measuring and testing made for vastly different outcomes in quality. Recognizing these differences as a barrier to trade, a group of delegates from 25 countries met to create the ISO, and the organization officially began operation on February 23, 1947. Each member nation participates through their national standards organization.

The United States is a member of the ISO through the American National Standards Institute (ANSI) (www.ansi.org). The collective efforts of ISO members have helped to make the development and production of products and services safer and more efficient.

Let's Explore!

Visit the ANSI website: http://www.ansi.org

a. What is the mission of ANSI?

b. Why is ANSI relevant to quality systems?

ISO 9000. Quality management is the primary concern of the ISO 9000 standard with its focus on product design, manufacturing, sales, and service. It is accepted in over 90 countries and applicable not only to product-focused organizations but service oriented organizations as well (e.g., hospitals). This standard strives to involve employees at all levels to participate in the quality process.

The guiding principle underlying the entire standard is ***transparency*****.** Every member of an organization should be able to communicate **what** they intend to do to address a quality issue, **do** what they say they are going to do and, **prove** through documentation, they carried through the plan, and have a continuous **improvement** plan.

ISO 9000 management categories:

1. Scope.
2. Normative Reference.
3. Terms and Definitions.
4. Quality Management System.
5. Management Responsibility.
6. Resource Management.
7. Production Realization.
8. Measurement, analysis, and improvement.

ISO 9000:2008. By the early 1990's, ISO 9000 was becoming increasingly outdated. The revision and improvement of the standard were a long, arduous process. The first round of major revisions was completed in 2000. The last round of additional revisions was finalized in 2008. Some of the features of the newly revised standard include integration of the **plan-do-check-act cycle** as a system standard, stronger emphasis on customer feedback in analyzing the quality process, and a complete overhaul of the language the standard is written in (about an eighth-grade level) for improved readability.

Eight fundamental principles of ISO 9001:2008 standards:

1. Customer-focused.
2. Leadership.
3. Involvement of people.
4. Process approach.
5. Systems approach to management.
6. Continual improvement.
7. Factual approach to decision making.
8. Mutually beneficial supplier relationship.

ISO 9000:2008 consists of three areas:

1. ISO 9000:2008, Quality Management Systems: Fundamentals and Vocabulary: Provides a standard of reference to the concepts and vocabulary used in ISO 9001:2008 and ISO 9004: 2008.
2. ISO 9001:2008, Quality Management Systems: Requirements: Intended for use by all organizations regardless of type, size or industry. Specifies requirements for achieving ISO certification.
   ISO 9001 Contains 4 Sections:
   1. *Management Responsibility:* Discusses the impact of data analysis on an organization's quality management system.
   2. *Resource Management:* Detailed documentation of resource availability and deployment specified as a certification requirement..
   3. *Product and/or Service Realization:* Specifies continual process improvement through self-assessment and customer requirements.
   4. *Measurement, Analysis & Improvement:* Methods of measuring system, processes, products or services.

3. ISO 9004:2008, Quality Management Systems: Guidelines for Performance Improvement: Not a requirement for certification. This standard specifies a means for those companies wishing to go beyond ISO 9001:2008 and develop a quality management system designed for continuous improvement of performance in all areas.

Documentation. A valid QMS requires rigorous documentation and disciplined record keeping. Some of the activities of record required by ISO 9000 include, but may not be limited to training records, policies, procedures, instructions, protocols, purchasing records, test data, audit records, and calibration records. ISO 9001 requirements on documentation are published in Document: ISO/TC 176/SC 2/N525R2, October 2008. ISO 9001:2008 clause 4.1 General requirements require an organization to *"establish, document, implement, and maintain a quality management system and continually improve its effectiveness in accordance with the requirements of this International Standard."* (www.iso.org)

Clause 4.2.1 explains that the quality management system documentation shall include:

1. A q***uality policy*** and ***quality objectives.***
2. A ***quality manual.***
3. Documented ***procedures***; established, documented, implemented and maintained.
4. Documented ***processes***; effective planning, operation and control of its processes.
5. ***Records*** required

QMS documentation differs from one organization to another relative to the size of the organization, the scope, and complexity of its activities in addition to many other factors such as federal regulations.

Quality Manual: The Company establishes and maintains a quality manual that includes:

1. The scope of the quality management system, in detail.
2. Procedures established for the quality management system, documented or referenced.
3. A description of the interaction between the processes of the quality management system.

Control of Records and Documents: All documents formally describing the QMS must be strictly controlled. No changes can be made to these documents without first passing through an official change procedure as outlined within the company's QMS. The company must establish a procedure to control everything from storage and retrieval of records to their identification, legibility, and disposal.

A documented procedure is established to define the controls needed to:

- ✓ Approve documents for adequacy before issue.
- ✓ Review and update as necessary and re-approve documents.
- ✓ Ensure that changes to documents are traceable
- ✓ Ensure that relevant versions of applicable documents are available
- ✓ Ensure that documents remain legible and readily identifiable.
- ✓ Prevent the unintended use of obsolete documents

ISO 14000. ***"Environmental management"*** *is the focus of the* ***ISO 14000*** *standard.* Environmental management can be loosely defined as the steps a company takes to minimize its impact on the natural environment and to continuously improve its environmental track by reducing harmful waste by-products from the manufacturing process.

Initially, the issue of environmental management was addressed only briefly in ISO 9000. As social and political attitudes towards environmental safety changed, the ISO organization decided to address the issue by creating a complete set of guidelines and standards. This new environmental management system is not a regulation or law (none of ISO's standards are). However, it does mirror the kinds of steps a company must take to come into compliance with local legislation and regulations. In other words, it provides a useful framework for businesses to follow when planning and implementing their own EMS. Some companies will even go a step further by requiring partners and suppliers to come into compliance with them. For example, Ford and GM both require their suppliers be ISO-14000 certified.

To become ISO 14000 certified, a company must:

1. Implement an Environmental Management System.
2. Assure compliance with existing laws and regulations.
3. Demonstrate a commitment to continual improvement.
4. Minimize waste.
5. Prevent pollution.

ISO 14001:2015

Anne-Marie Warris, Chair of ISO/TC 207/SC1, the technical committee that developed the standard and revision believes *"the new version helps with a stronger integration between environmental issues and an organization's strategic action planning and thinking."* **ISO 14001:2015 key components include:**

- ✓ Factoring in both external and internal elements that influence their impact
- ✓ A greater commitment from leadership
- ✓ An increased alignment with strategic direction
- ✓ Increased protection for the environment, with a focus on proactive initiatives
- ✓ More efficient communication, driven by a communications strategy
- ✓ Life-cycle thinking, considering each stage of a product or service, from development to end-of-life

ISO/IEC Standards for Testing Laboratories. Testing and calibration laboratories follow the ***ISO/IEC 17025 standard***. This standard is very similar to ISO 9000 but addresses the additional issue of competence as it applies to creating and maintaining a quality system the laboratory to produce valid results. Greater emphasis on the responsibilities of senior management and communication with customers became a part of this standard in its 2005 revision.

The five top elements of ISO/IEC 17025:

1. Scope.
2. Normative references.
3. Terms and Definitions.
4. Management requirements.
5. Technical requirements.

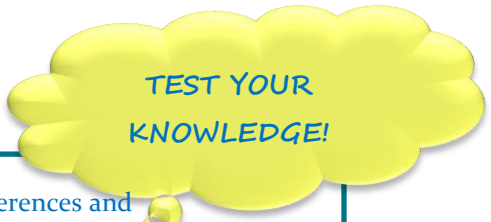
Further information including other relevant laboratory testing ISO guidelines are listed at the American Association for Laboratory Accreditation (www.a2la.org):

- ISO/IEC17025 Testing/Calibration Laboratories
- ISO/IEC17020 Inspection Bodies
- ISO/IEC17043 Proficiency Testing Providers
- ISO/IEC17065 Product Certification Bodies
- Clinical Testing Laboratories
  - ISO 15189
  - CLIA Requirements
  - CLIA and ISO 15189
- ISO Guide 34 Reference Materials Producers

ISO DEVICE REGULATIONS ISO 13485

ISO13485 is the standard for a quality management system for the design and manufacture of medical devices. This standard (although a stand-alone document) is harmonized with ISO 9001 with the exception that 13485 need only demonstrate the quality system is implemented and maintained whereas 9001 requires a continual improvement aspect.

ISO Clinical Practices and Devices. The medical device industry is quickly becoming a major player in the medical biotechnology industry. Moreover, regulations governing them can be complicated due to their unchartered territory as well as their multi-disciplinary applications. For example, what regulations would apply to an ocular device inserted into the eye (medical device), which measures and responds to eye pressure (diagnostic) to release a particular quantity of drugs (drug)? As you can imagine, global regulations vary widely. To address this ISO and the European Committee for Standardization (CEN) worked together to come up with comprehensive clinical study regulations governing devices. **ISO 14155** addresses these procedures including, risk assessment, ethical issues, constructing protocols and scientific conduct to name a few. More on this ISO regulation in following chapters that delve into devices and clinical studies.



GMP versus ISO: Presented below is a table that compares and contrasts the differences and similarities between regulations and ISO 9000 standards. Fill in the missing parts of the table

GMP	ISO
Mandatory system	
Federal (US) Law	
	Can apply to any industry
Enforced by FDA	
Standards are generic and broad in scope but apply to the pharma/medical industry only	
Standards rely heavily on testing and inspection; functional areas are clearly defined	Standards rely on management commitment, systems, procedures, and documentation; quality system needs to be only as comprehensive as necessary
	Compliance is monitored by outside auditors paid by the company

ISO Certification. The process of obtaining certification is expensive, complicated, and time-consuming. To receive certification, a company must hire an independent, certified auditor (registrar) to perform an audit of the company's QMS.

For a company to get certification, they must first create a quality system (described in their quality manual), create all the systems and documents and put them in place (implementation). The company then hires a certified ISO auditor that audits the business to ensure all of their systems and documentation are in place. The company then has to apply for ISO certification and maintain the process.

The largest and most frequent obstacle for most businesses is coming into compliance with the documentation process. Eventually, however, certification pays for itself through the product quality benefits it provides. Processes can be streamlined and improved by coming into compliance. Additionally, consumer confidence in a product goes up with the ISO 9001 label and gives the company a definite competitive advantage.

Standards for Pharmaceutical Companies: Published in March 2006, ***ISO 15378 is a standard specifically developed for suppliers of pharmaceutical primary packaging.*** The standard specifies the QMS requirements necessary to demonstrate an organization's ability to provide primary packing materials for medicinal products that meet customer requirements. It also defines the applications for design, manufacture, and supply of primary packaging materials. It also guarantees that the legal requirements and the standards of the pharmaceutical industry for medical devices are met and that the company operates on an effective and efficient quality management system.

ISO 15378 Key Areas:

1. Risk analysis
2. Checking / qualification / validation
3. Manufacturing tools
4. Computerized systems
5. Contamination risk & cleanliness control
6. Traceability
7. Change control
8. Operators training in GMP practices

TEST YOUR KNOWLEDGE!

1. Since ISO 9000 certification and compliance are voluntary, what motivates companies to adopt these stringent quality standards? Read the following article: https://www.iso.org/news/2006/03/Ref998.html

2. In your own words, explain why you would want or need to have a voluntary standard such as ISO 15378 when the pharmaceutical industry is already following FDA-regulated CGMP.

3. In your own words, compare the issues addressed by the following standards. You may be brief (2-3 sentences) each.

ISO Standard	Issue addressed by this standard
ISO 9001:2008	
ISO 9004:2008	
ISO 14000:2015	
ISO/IEC 17025	
ISO 15378	
ISO 13485	
ISO 14155	

OTHER VOLUNTARY QUALITY MANAGEMENT SYSTEMS

Six Sigma. As products become more complex, so does the manufacturing processes to manufacture them. This high complexity resulted in higher failure rates in manufacturing. In the 1990s Bill Smith of Motorola Corporation developed Six Sigma as a strategy to deal with these failures and improve profitability by reducing process and product variation. In 2005, Motorola attributed $17 billion dollars in savings from implementing the Six Sigma system!

Six Sigma is a rigorous process improvement methodology encompassing a procedure of Define, Measure, Analyze, Improve, Control (DMAIC). The DMAIC method encourages employees at all levels in the company to accept feedback, utilize clearly defined metrics, collect and analyze data, and create an overall company culture built on trust.

The overall goal of Six Sigma is to reduce variation in the process, and the product, and thereby defects by using a highly focused system of problem-solving. The term Six Sigma stems from manufacturing terminology using statistical process modeling. A sigma rating is the yield or percentage of a defect-free product; six sigma is a process in which 99.99966% of the products manufactured are statistically free of defects (3.4 defective parts per million). Several features set Six Sigma apart from other methodologies; there is a clear focus on measurable, fiscal returns on a project, and there is an increased commitment make databased decisions and statistical methods.

Six Sigma (Define, Measure, Analyze, Improve, Control) (Penfield, 2014)

The DMAIC methodology:

- ✓ Define the project and goals of the project
- ✓ Measure the current process using data
- ✓ Analyze the data using cause-and-effect method to seek out the root cause of the defect
- ✓ Improve the process based on the data and analysis; perform pilot runs
- ✓ Control the process by ensuring deviations are corrected; implement statistical process control, continuously monitor process

Lean Manufacturing. Lean is a manufacturing philosophy focused on waste removal developed by Toyota Production Systems (TPS) and popularized by the book *"The machine that changed the world."* Lean seeks ways to improve the production process to accomplish more with less time, space and resources. Elimination of waste is the centerpiece of this quality approach.

The lean approach recognizes seven forms of waste:

1. Defective parts
2. Producing more parts than needed
3. Excessive inventory
4. Unnecessary steps/activities
5. Unnecessary movement
6. Unnecessary handling of materials
7. People waiting

5S. One important waste-eliminating quality system that is commonly implemented in biotechnology companies (such as Life Technologies) is the 5S system.

5S Method (Musinik)

This system relies on visual cues to achieve an orderly workplace, and eliminates waste in the form of unnecessary steps, activities, movements, waiting around, and excess inventory. The 5S system – Sort (*Seiri*), Set in Order (*Seiton*), Shine (*Seiso*), Standardize (*Seiketsu*) and Sustain (*Shitsuke*) - provides a

system for organizing, cleaning, developing and maintaining the work environment to minimize waste. https://youtu.be/jPXYa3FQP8k

The method encourages workers to participate in improving their workplace and process. Learn more about 5S system here: http://leanmanufacturingtools.org/192/what-is-5s-seiri-seiton-seiso-seiketsu-shitsuke/

Let's Explore

Watch the following video to learn more about the 5S system. Using the 5S system, how can you organize your home office area to minimize waste in your studies? Identify the 5S for improvement. What is the benefit of 5S? https://youtu.be/dDqmCJfodeo

Summary

Regardless of the approach of the quality system - CGMP, ISO, Six Sigma, 5S, Lean –these systems participate in product quality by establishing a comprehensive quality system that stresses the eight fundamental principles to quality management:

1. Customer focus
2. Process Improvement
3. Fact-based decision making
4. Systems approach (tracking)
5. Leadership commitment to excellence
6. Involvement of all employees
7. Continuous improvement
8. Mutually beneficial supplier relationship

CHAPTER 4: THE FOOD & DRUG ADMINISTRATION

Objectives

- ✓ Explore the origin of regulations in the U.S.
- ✓ Discuss the role and organization of the Food and Drug Administration
- ✓ Identify products the FDA has regulatory authority
- ✓ Explore the various FDA offices & Centers responsible for product approval
- ✓ Distinguish between CFR, Guidelines, and Points to Ponder
- ✓ Demonstrate the use of eCFR database to locate regulations

CONSUMER SAFETY AND HEALTH:

The idea of protecting the safety and health of consumers isn't new. There were many societies, such as ancient Rome, where the penalties for producing an unsafe product were quite harsh. In contrast, our modern day society's view of regulations and protections is that of prevention. Of course, there are still "after-the-fact" remedies available to the consumer. However, regulations in modern day are designed to build quality and safety into the production process, thereby limiting if not eliminating health and safety concerns before the product reaches the consumer. In this chapter, we will examine some of the most significant regulations, explore how regulations come to pass, and discuss the role of the Food and Drug Administration (FDA) in regulations of consumer products.

HISTORY OF REGULATIONS IN THE PHARMACEUTICAL INDUSTRY

The aim of pharmaceutical regulation is to ensure objective characteristics such as safety, effectiveness, honesty in labeling, accurate reporting of side effects (if any). *Regulations do not apply to subjective characteristics* such as taste, color or texture. There are no regulations, for example, that dictate all aspirin tablets be blue in color. Most of us take quality for granted these days. It was not so long ago that substances such as cocaine could be used as ingredients in soda (Coca-Cola) or over-the-counter tonics (Wikipedia, 2016). The FDA outlines major milestones of product regulation here.
https://www.fda.gov/AboutFDA/WhatWeDo/History/Milestones/ucm128305.htm
Some of the better-known incidences and the regulations that arose, as a result, are as follows:

- The original *Food Drug and Cosmetic Act (FDCA)* of 1906. The FDCA is intended to prevent the sale of unacceptable foods and drugs (e.g., meat processed in filthy factory conditions) rather than regulate safety or effectiveness.
- The Durham-Humphrey Amendment, passed in 1951, was the first federal law requiring a physician's prescription for drugs "unsafe for self-medication."
- The requirement that drugs are proven to be both safe and effective before release and that such effectiveness is supported by "substantial evidence" is the mandate of the Kefauver-Harris Amendments.
- The *Orphan Drug Act* amended the *FDCA* as of January 4, 1983, is an act calling for incentives to companies producing orphan drugs (which benefit only a small percentage of the population and unprofitable).
- *The Drug Price Competition and Patent Term Restoration Act,* passed in 1984, made generic drugs more readily available at the same time as providing a way for manufacturers to recoup some amount of pre-patent research costs by factoring research time into the patent life of the drug
- ClinicalTrials.gov was founded in 1999 to provide the public with updated information on enrollment in federally and privately supported clinical research.

Let's Explore!

Go here to explore more FDA law milestones. List any laws put in place after 2005. Why do you think they were put into law? Are there any unusual laws?

WHAT CAUSES REGULATIONS TO BE ENACTED?

There are two major influences which trigger the enactment of regulations:

1. Consumer tragedy (serious injury, death) resulting from the use of a product
2. Advancements in science and technology

Once alerted to either of the above conditions, our lawmakers respond by passing the needed legislation, and enforcement of the law is assigned to the appropriate government agency. The issue of enforcement is not always clear-cut. Several agencies may enforce regulations in certain sectors – for example, GMOs, which we will discuss in a later chapter. Authority for oversight and regulation of the pharmaceutical industry, however, is quite clear - the primary agency is the Food and Drug Administration (FDA).

Let's Explore!

Go to the following website to learn how consumers can report problems with FDA-regulated products. https://www.fda.gov/Safety/ReportaProblem/default.htm Look to the Q&A on the left-hand panel - what kinds of products *doesn't* the FDA handle?

THE FOOD AND DRUG ADMINISTRATION (FDA)

The FDA (www.fda.gov) is an administrative agency created to regulate food and drug supplies in the United States for the safety and health of its citizens. *FDA is an agency within the Department of Health and Human Services.* https://www.hhs.gov/ It should be noted that the FDA has traditionally focused on the US markets, however, with the global market growth (of imports and exports of products and raw materials) the FDA now manages over 2 trillion dollars of goods manufactured in over 150 nations worldwide (FDA, FDA Global Engagement report, 2016).

INTERNATIONAL HARMONIZATION EFFORTS

What happens when a biotechnology company based in the United States or any other country wants to expand to overseas marketplaces? Conflicting regulatory standards made trade difficult until an effort began in the 1990's to harmonize international standards so that important medical products could be bought and sold with less regulatory 'red tape.' *The FDA has been the leader in this effort both in the U.S. and around the globe. The FDA assists both foreign and domestic manufacturers in compliance with CGMP, CGP, GLP, Safe and Sanitary Processing and other regulations.* (http://www.fda.gov/ForIndustry/default.htm).

Let's Explore!

Visit the FDA website and select each tab at the top of the page. Each tab corresponds to each of the different types of products the FDA regulates. Briefly, describe the eight types of products that the FDA regulates:

PRODUCT	DESCRIPTION
Drugs	A substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease. The site includes drug approval, safety, availability, regulatory information, research and consumer information relating to drugs

ORGANIZATION

The FDA is vast and complex. A complete organizational chart (2017) is found on their website here. https://www.fda.gov/aboutfda/centersoffices/organizationcharts/ucm393155.htm A summary of FDA history and organization can be found here. https://www.fda.gov/AboutFDA/WhatWeDo/History/default.htm

The FDA, like most organizations, change with changing the economy, world harmonization and emerging technologies and products. *The current hierarchy consists of the Office of the Commissioner overseeing five offices and directorates. Those offices oversee eight centers*. Similar to the federal government, the FDA possesses the following powers:

- Legislative: The FDA has the authority to create and issue rules.
- Executive: The FDA has the power to conduct investigations.
- Judicial: The FDA has the jurisdiction to review evidence and make judgments on a product.

The FDA has "product centers" headquartered; largely in the Washington, D.C. area, (the NCTR is located in Jefferson, Arkansas). FDA "field offices" are located throughout the United States. The field offices are "the eyes and ears" of the FDA, and it is from these offices that operational personnel enforce the law.

FDA FIELD OFFICES

Office of the Commissioner: Leadership of the agency's scientific activities, communication, legislative liaison, policy and planning, women's and minority health. (fda.gov)

- About the Office of the Commissioner
- Commissioner's Page
- Immediate Office of the Commissioner
- National Center for Toxicological Research

Office of Foods and Veterinary Medicine: Leads a functionally unified FDA Foods Program that addresses food and feed safety, nutrition, and other critical areas to achieve public health goals.

- Office of Foods and Veterinary Medicine
- Center for Food Safety and Applied Nutrition
- Center for Veterinary Medicine

Office of Global Regulatory Operations and Policy: Provides leadership for FDA's domestic and international product quality and safety efforts.

- Office of Global Regulatory Operations and Policy
- Office of International Programs
- Office of Regulatory Affairs

The FDA's Office of Regulatory Affairs (ORA) leads all FDA field activities and provides FDA leadership on imports, inspections, and enforcement policy.
https://www.fda.gov/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/default.htm
ORA supports the agency in the following ways:

- ✓ By inspecting regulated products and manufacturers.
- ✓ Performing sample analysis on regulated products.
- ✓ Reviewing imported goods.
- ✓ Developing policies on compliance and enforcement.
- ✓ Executing the FDA's Import Strategy and Food Protection Plans.

Office of Medical Products and Tobacco: Provides advice and counsel to the Commissioner on all medical product and tobacco-related programs and issues.

- Office of Medical Products and Tobacco
- Center for Biologics Evaluation and Research
- Center for Devices and Radiological Health
- Center for Drug Evaluation and Research
- Center for Tobacco Products
- Office of Special Medical Programs

Office of Operations: Provides agency-wide services including information technology, financial management, procurement, library services, and freedom of information, FDA history, and facilities.

- Office of Operations
- Office of Equal Employment Opportunity
- Office of Finance, Budget, and Acquisitions
- Office of Information Management and Technology
- Office of Management

The Office of International Programs leads the FDA's international effort is divided into five distinct staffs:

- Office of the Director
- International Agreement Staff
- International Relations Staff
- International Scientific Activities and Standards Staff
- International Planning and Resources Management Staff

A list of their duties can be found here. https://www.fda.gov/InternationalPrograms/default.htm Other highlights in the international arena include the Mutual Recognition Agreement with the European Union and the development of the final version of the Common Technical Document that is being used to seek new drug approval in the U.S., the European Union and in Japan.

FDA PRODUCT CENTERS

Now, let's examine more closely the functions of several important product-oriented centers: CDER, CBER, CDRH, CVM, CTP, NCTR, and CFSAN.

Center for Drug Evaluation and Research (CDER): The CDER oversees the regulation of drugs. The official definition of a drug is *"an article intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; articles designed to affect the structure or any function of the body of man or other animals."* (FDA, 2016) CDER regulates over-the-counter and prescription drugs, including biological therapeutics (act as drugs), and generic drugs. This work covers more than just medicines. For example, fluoride toothpaste, antiperspirants, and dandruff shampoos are all considered "drugs." Why? More on this in a later chapter!
https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/

Center for Biologics Evaluation and Research (CBER): The CBER oversees the regulation of biologics. The official definition of a biological product is *'any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product'* (FDA, 2016). More information on a biologic in the following video. Note, therapeutic biologics are biologics that act like drugs and therefore are overseen by CDER instead. More on this in a later chapter!
https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/

Center for Devices and Radiological Health (CDRH): Oversees the regulation of medical devices and radiation-emitting products, and also includes biotechnology products used in diagnostics, such as HIV or pregnancy tests. You will be surprised to learn about some unusual products that are considered medical devices. https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/

Center for Veterinary Medicine, and (CVM): The CVM is a product center, which oversees regulation of food, food additives, drugs and biologics for animals. They also conduct research that helps FDA ensure the safety of animal drugs, food for animals, and food products made from animals, however, they do not oversee pre-clinical animal studies. Those fall under the purview of the product center of the product the pre-clinical studies are for. Here is a video on the CVM put out by the FDA.
https://www.fda.gov/AboutFDA/CentersOffices/OfficeofFoods/CVM/ucm245225.htm

Center for Food Safety and Applied Nutrition (CFSAN): CFSAN oversees food safety and purity. It has the power to regulate all domestic and imported food *except for meat, poultry, and eggs* (USDA regulates those). They oversee the safety of food ingredients developed through biotechnology, dietary supplements, food additives, and proper labeling of food. CFSAN is also concerned with food contamination, such as biological pathogens and naturally occurring toxins.

Center for Tobacco Products (CTP): The Center for Tobacco Products (CTP) oversees the implementation of the Family Smoking Prevention and Tobacco Control Act. Some of the Agency's responsibilities under the law include setting performance standards, reviewing premarket applications for new and modified-risk tobacco products, requiring new warning labels, and establishing and enforcing advertising and promotion restrictions. (fda.gov)

National Center for Toxicological Research (NCTR): FDA's research center conducts peer-reviewed research and develops new scientific tools for FDA to improve public health. This research produces innovative tools to assist in solving complex health issues, anticipated toxicological problems, and enhances the science of regulatory decision-making at the FDA. The NCTR publishes an annual report outlining their projects and can be found here: https://www.fda.gov/AboutFDA/CentersOffices/OC/OfficeofScientificandMedicalPrograms/NCTR/ResearchAccomplishmentsPlans/default.htm

Go to this website for a tutorial about the Food and Drug Administration. Scroll down and press on the sound icon to hear videos. At the very bottom of the page is a self-quiz. Briefly, summarize the mission of the FDA. Briefly, outline the primary duty of each of the following FDA offices:

Center or Office	Summary of Main Duties
CFSAN	
CDER	
CBER	
CDRH	
CVM	
NCTR	
ORA	
CTP	

ADJUDICATION, RULEMAKING, GUIDELINES, AND POINTS TO CONSIDER

The primary administrative activities of the FDA are rulemaking and adjudication.

Rulemaking affects both the public and the drug and device manufacturers. When new rules are proposed, the FDA publishes them electronically in the code of federal regulations (CFR), which is available to the public at www.ecfr.gov. Adjudication is the term used to describe how the FDA responds to requests for approval to investigate or market a product. The FDA reviews each submission as a separate case even if each submission refers to the same product. Upon conclusion of its review, the FDA responds with its disposition or order.

Federal regulations are first published in the Federal Register (FR) by the executive departments and agencies of the Federal Government published every business day by the National Archives and Records Administration (NARA). https://www.archives.gov/federal-register/the-federal-register/about.html

The Federal Register is a legal newspaper where the public is given notice of proposed new rules and intended actions, allowing time for comment. When the FDA finalizes a rule, it publishes its response to public comments in a preamble to the rule.
This bureaucratic process is quite time-consuming and, therefore, the FDA employs two additional methods of transmitting information to the public and industry: Guidelines and Points to Consider which are published on the FDA website. *Neither the Guidelines nor the "Points to Consider" represent any legal regulation and may be challenged by scientific or other types of evidence.*

- ✓ Guidelines represent the FDA's formal position on long-standing issues. Guidelines also communicate procedures or standards of general applicability that are acceptable to the FDA.
- ✓ Points to Consider are intended to disclose the FDA's current position on any area considered new or rapidly changing, such as some parts of the biotechnology industry. In other words, the FDA has not formulated a formal stance.

THE CODE OF FEDERAL REGULATIONS (CFR)

The CFR is a massive set of regulations, published annually, where all the federal agencies post their rules. It provides information (based on quality techniques) on quality systems in the laboratory (QSR), manufacturing practices, laboratory practices, and clinical practices. Due to the sheer volume of information available through the CFR, it is useful to know how it is organized.

CFR Organization

- Titles represent broad areas subject to Federal regulations.
- Titles are divided into chapters that are assigned to various federal agencies.
- Chapters are divided into parts covering specific regulatory areas.
- Each part or subpart is then divided into sections – the basic unit of the CFR.
- Sometimes sections must be subdivided further into paragraphs or subsections.

21 CFR OVERVIEW

PART	COVERS
100 series	Food – 110 CGMPs; Dietary supplements – 111 CGMPs
200 & 300 series	Pharmaceuticals – 210 & 211 CGMPs
500 series	Animal feeds & medications
600 series	Biological products – 606 CGMPs
700 series	Cosmetics (limited regulations)
800 series	Medical Devices
900 series	Mammography quality requirements
1000 series	Radiation emitting device
1200 series	Non-FD&C Act Rulings
Other	GLP-58; GCP-50,54,56; Electronic records-11

CFR Title 21 Chapter 1: FOOD & DRUGS

Title 21 Chapter 1 of the CFR contains all regulations concerning the safe production of food, drug, medical device, diagnostic, and biologic products for human and animal use under FDA supervision. The 21 CFR regulations can be accessed at the following: http://www.ecfr.gov

Go into the eCFR database, in the pull-down menu choose Title 21 and press 'go.'
Click on parts 200. https://www.ecfr.gov

1. What is the part of labeling?
2. What is the subpart for labeling requirements for over the counter drugs?
3. What are the content requirements for OTC drug product labeling?

SIGNIFICANT 21 CFR REGULATIONS IN THE BIOTECHNOLOGY SECTOR

- 21 CFR 11: Electronic Records; Electronic Signatures
- 21 CFR 201: Labeling
- 21 CFR 314: Applications for FDA Approval to Market a New Drug
- 21 CFR 610: General Biological Product Standards
- 21 CFR 803: Medical Device Reporting
- 21 CFR 1271: Human Cells, Tissues, & Cellular and Tissue-based Products

CURRENT GOOD MANUFACTURING PRACTICES (CGMPS)

GMP regulations are included in Title 21 Chapter 1 of the CFR, in three regulations dealing with different types of manufactured products:

- for drugs (21 CFR 211)
- for medical devices (21 CFR 820)
- for blood and blood components (21 CFR 606)

The general principles of CGMP that all these regulations have in common:

- ✓ Quality, safety, and effectiveness are designed and built into the product, not tested or inspected into the product.
- ✓ Each step in the manufacturing process is documented and controlled to ensure the finished product meets design and compendia specifications.
- ✓ Process documentation provides evidence of compliance with CGMPs.

Three primary criteria used by FDA in the design of these CGMP regulations:

1. Regulations should contain objectives and not detailed specifications. They should allow latitude for different manufacturers to find their own means of compliance.
2. Regulations should contain requirements that are considered feasible and valuable as recognized and considered by experts as assuring quality.
3. If a practice can be established to be achievable and useful, then it can be required even though it does not exist in the regulations.

Setting standards for quality in the biotechnology industry is difficult due to the often new and complex manufacturing processes involved. How should the FDA set quality standards, for example, for chromatographic purification systems? These processes are difficult to validate and represent 'gray' areas where quality regulations are concerned. For this reason, companies frequently rely on regulations that the FDA has not yet finalized, and they comply voluntarily with CGMPs and Guidelines.

21 CFR 58: GOOD LABORATORY PRACTICES (GLPS)

Animal studies of pharmaceutical products are regulated by Good Laboratory Practices (GLP) as covered in 21 CFR 58. These regulations came about in 1975 because of an FDA inspection of several testing laboratories where conditions were, frankly, appalling and animals treated inhumanely. Any laboratory wanting to run animal tests today must maintain clean, adequate facilities, provide proper care for the animals and conduct valid tests. *All non-clinical safety studies of new drugs and new drug applications, drug biologics, veterinary drugs, and some food additives fall under the purview of GLP regulations.*

GOOD CLINICAL PRACTICES (GCP)

Good Clinical Practices (GCPs) are a similar set of standards that apply to human subjects of clinical trials and experiments. We will discuss clinical studies in a later chapter, however, briefly touch on the basics here.

Regulatory History of GCPs:

- By the 1980s, it became apparent that representative populations needed to be included in clinical trials - factors that may influence the effectiveness and side effects of drugs include age (children, older patients), sex, and even ethnicity!
- In 1989, the FDA issued guidelines asking manufacturers to determine whether a drug is likely to have significant use in older people

- In 1993, the FDA issued the Gender Guideline, which called for assessments of medication responses in both sexes.
- In 1998, the FDA required that a marketing application analyze data on safety and effectiveness by age, gender, and race; called the Demographic Rule.
- In 2002, the Best Pharmaceuticals for Children Act was passed to improve the safety and effectiveness of medicines for children.
- In 2003, the FDA was given clear authority under the Pediatric Research Equity Act to require drug sponsors to conduct clinical research into pediatric applications for new drugs.

Clinical Studies. *Although there is no regulation specifically entitled "Good Clinical Practice," there are several regulations, which govern the conduct of clinical trials.*

- Volunteers participating in a clinical study must be able to give informed consent. Informed consent means educating each potential subject on the treatment they are to receive as a part of the study as well as any risks that may be associated with their participation. FDA regulations entitled "Protections of Human Subjects" (21 CFR 606) set forth the requirements for informed consent.
- Clinical trials must be reviewed by a committee independent of the study sponsor called an Institutional Review Board (IRB) (21 CFR 50). The regulations specify the organization and personnel who make up this board, as well as the records and reports that are to be kept.
- *21 CFR 312 Subpart D outlines the responsibilities of trial sponsors and investigators during a trial.* Additionally, the FDA "Guideline for the Monitoring of Clinical Investigations" explains monitoring and documentation.

In summary

- ✓ The role of the FDA is to ensure public safety and health
- ✓ Consumer tragedy and advancements in science are two major influences that trigger regulations in the US
- ✓ The FDA is an agency within the Department of Health & Human Services, with the Office of the Commissioner overseeing five offices, and eight centers
- ✓ CDER oversees regulation of drugs; CBER, biologics; CDRH, Medical Devices; CVM, animal drugs and food; and CFSAN, food safety
- ✓ 21 CFR Chapter 1 contains CGMP regulations concerning safe production of food, drug, medical devices, diagnostic kits, and biological products for human and animal use under FDA purview

CHAPTER 5: GOOD GUIDANCE PRACTICES (GXPs)

Objectives

- ✓ Demonstrate the ability to research Good Guidance Practices companies must follow when manufacturing biotechnology products
- ✓ Differentiate between GMP, GCP, GDP, and GLP
- ✓ Explore Good Laboratory Practices as they apply to animal testing labs
- ✓ Describe the process for clinical studies and how Good Clinical Practices contribute to safe, effective and ethical studies. Demonstrate the use of clinical studies website to research current and past clinical studies.
- ✓ Understand Current Good Manufacturing Practices, how to research regulations relating to CGMPs, and the basic principles the FDA uses when adopting CGMPs.
- ✓ Understand what CAPA is and why it is so essential to the FDA and CGMPs.
- ✓ Explore different quality documents used in biomanufacturing
- ✓ Identify different types of documentation and apply their importance to a QMS and CGMPs.

GOOD GUIDANCE PRACTICES

Guidance documents (and guidelines) are used to relate the FDA current regulatory principles and practices for the manufacturing of products. In the previous chapter you were introduced to some of the good practices that the FDA regulates along with their CFRs; Current Good Manufacturing Practices, Good Laboratory Practices, and Good Clinical Practices. In this chapter, we will extend it to Good Documentation Practices as well, and discuss some of the more relevant documents to regulatory affairs.

GOOD LABORATORY PRACTICES (GLPS)

Good Laboratory Practices (GLPs) came about in the 1970s to improve the confidence of drug safety data for non-clinical laboratory studies. These regulations define the quality system used in non-clinical studies and are meant to ensure the integrity and accuracy of study data as well as the framework for the conduct and reporting of nonclinical laboratory studies. Non-clinical studies are typically performed on animals and focus on safety testing of drugs that intend to go through human clinical trials.

Animal studies of pharmaceutical products are regulated by GLP and came about as a result of a 1979 FDA inspection of several testing laboratories were conditions were, quite frankly, appalling, and the animals were treated inhumanely. Any laboratory wanting to run animal tests today must maintain clean, adequate facilities, provide proper care for the animals and conduct valid tests. *All non-clinical safety studies of new drugs and new drug applications, drug biologics, veterinary drugs, and some food additives fall under the purview of GLP regulations.*

GLPs are regulated by the FDA through the FD&C Act in addition to the Public Health Service Act (PHS Act). Both acts work together to ensure the customer receives a product that is both safe and effective. Human clinical trials are not covered by GLPs as well as preliminary feasibility studies do not have to be conducted under GLP (unless they are performed in animals). *Data obtained from non-clinical studies followed under GLPs will be submitted to the FDA to support a product's overall safety claims*. Most FDA centers provide additional directed GLP communication and guidance documents that are unique to the products they oversee. Currently, GLPs are provided by CDER, CBER, CDRH, CVM, and CFSAN.

Bioanalytical specimen handling and analysis is not covered by CLIA. The FDA has provided guidance documents that outline bioanalytical testing which must include the following validation parameters: accuracy, precision, selectivity, sensitivity, reproducibility, and stability. It's important to note that these validation parameters should be sought for all GLP method validation practices.

GLP REGULATIONS & GUIDELINES

In the drug development process, non-clinical studies are performed before an application to perform human studies is submitted. The key elements of a non-clinical study protocol include:

- Facility where the study is conducted
- Standard Operating Procedures (SOPs)
- Personnel involved
- Equipment used
- Drug being studied
- Biological system the drug will be tested
- How you will plan to document the study
- How you will retain the records

GLPs are regulated by FDA 21 CFR Part 58 and include:

- Toxicology studies in laboratory animals
- Medical device safety testing
- Biochemistry, immunology & microbiology testing
- Eye, dermal and muscle irritation studies
- Pharmacology studies
- Bioanalytical studies
- Color and food additive safety
- Validation of methods for sample analysis

The FDA GLP regulations are divided into subparts to cover key GLP compliance elements and include:

- Subpart A: General Provisions
  - Type of products regulated, by agency that must comply with GLPs
- Subpart B: Organization and Personnel
  - Personnel must have appropriate qualifications (education, training & experience)
  - Includes Quality Assurance Unit – ensures compliance and conformance with regulations
- Subpart C: Facilities
  - All facilities must be of appropriate size and suitable for study
- Subpart D: Equipment
  - Equipment is designed appropriately, and function as intended for the study protocol – this includes maintenance and calibration of equipment
- Subpart E: Testing Facilities Operation
  - Test methods, equipment calibration, maintenance, and operation – SOPs.
  - Animal handling instructions and expectations
- Subpart F: Test and Control Articles
  - Chain of Custody
- Subpart G: Protocol for and Conduct of a non-clinical Laboratory study
  - Formal written plan (study protocol) instructions
  - Basic study documentation including Good Documentation Practices (see below)
- Subpart J: Records & Reports
  - What is needed in the final study report and how the study records will be stored

INSPECTION & ENFORCEMENT OF GLP LABORATORIES

The FDA may inspect any GLP laboratory to ensure they are following GLP regulations, its physical capabilities in supporting the study, personnel qualifications and training, and equipment. They may perform a routine or surveillance inspection, or they may have a cause to inspect. The primary objectives are outlined in the Bioresearch Monitoring Compliance Program (BIMO) include, verify the integrity of data, inspect non-clinical laboratory every two years conducting safety studies, and audit safety studies. More on inspection and enforcement in a later chapter.

It's important to note that following GLPs does not inherently mean your results will not have errors and your facilities will not have issues. *The value of GLPs is setting up the framework to strengthen your study, and increase oversight, and thereby provide confidence in study results*. Keeping excellent and retrievable records provide inspectors and auditor's easy access to study data to ensure data is accurate, traceable and complete.

GOOD CLINICAL PRACTICES (GCP)

The government has an interest in protecting the public from defective products and drugs. Therefore, companies must demonstrate their effectiveness and safety before mass distribution. However, the only way they can actively do this is by actually having human subjects test out their products.

If a potential new product appears safe in animal studies, then a plan is created to investigate the product in clinical trials using human volunteers. The company submits their plan to the FDA in an IND. The IND application includes a description of the product, the results of animal tests, and the plans for further testing. The FDA then decides whether the company's materials are sufficiently complete that the company can begin testing the product in humans.

Let's Explore!

Watch this video on clinical trials https://youtu.be/pm1igf85u0A

Good Clinical Practices (GCPs) apply to the performance of clinical trials of drug safety and efficacy in human subjects. GCPs aim to protect the rights and safety of human subjects and ensure the scientific quality of the studies. Clinical trials are conducted in stages, and each stage must be successful before continuing to the next phase. *Good Clinical Practices (GCPs) are a similar set of standards that apply to human subjects of clinical trials and experiments.*

Regulatory History of GCPs, from fda.gov website:

- The Nuremberg Code lists ten basic moral, ethical and legal principles outlining medical research established in response to the Nuremberg doctor's trials in 1946. This tribunal launched criminal proceedings against physicians for crimes against humanity in WWI.
- In 1964, the World Medical Association established ethical guidelines for biomedical research in humans called the Declaration of Helsinki. These guidelines include essential codes of conduct including areas involving informed consent, confidentiality, research protocol review, risk versus benefit analysis, publication and data access to the scientific community, and the importance of the subject's health being held over the interest of study.

- The Belmont Report in 1979 established principles of ethical research emphasizing respect for persons, beneficence, and justice. This lead to the Common Rule in 1981.
- By the 1980s, it became apparent that representative populations needed to be included in clinical trials - *factors that may influence the effectiveness and side effects of drugs include age (children, older patients), sex, and even ethnicity!*
- In 1989, the FDA issued guidelines asking manufacturers to determine whether a drug is likely to have significant use in older people
- In 1993, the FDA issued the Gender Guideline, which called for assessments of medication responses in both sexes.
- In 1998, the FDA required that a marketing application analyzes data on safety and effectiveness by age, gender, and race. This is known as the Demographic Rule.
- In 2002, the Best Pharmaceuticals for Children Act was passed to improve the safety and effectiveness of medicines for children.
- In 2003, the FDA was given clear authority under the Pediatric Research Equity Act to require drug sponsors to conduct clinical research into pediatric applications for new drugs.

Let's Explore!

Perform a cursory internet research on Tuskegee Syphilis Study (1932-1972). Summarize why this incident would cause outrage and a public apology by a US President? In what ways did this violate the Declaration of Helsinki? What was the regulatory response? (Meaning, what law was passed?)

WHAT ARE GOOD CLINICAL PRACTICES?

Although there is no regulation specifically entitled "Good Clinical Practice," there are several regulations, which govern the conduct of clinical trials.

- Volunteers participating in a clinical study must be able to give informed consent. This means educating each potential subject on the treatment they are to receive as a part of the study as well as any risks that may be associated with their participation. FDA regulations entitled "Protections of Human Subjects" (21 CFR 606) set forth the requirements for informed consent.
- Clinical trials must be reviewed by a committee independent of the study sponsor called an Institutional Review Board (IRB) (21 CFR 50). The regulations specify the organization and personnel who make up this board, as well as the records and reports that are to be kept.
- *21 CFR 312 Subpart D outlines the responsibilities of trial sponsors and investigators during a trial.* Additionally, the FDA "Guideline for the Monitoring of Clinical Investigations" explains monitoring and documentation.

Explore MedWatch on FDA website. Then, watch this FDA presentation on MedWatch:

1. What is MedWatch? Why are they are important?
2. Look through the safety alerts for human medical products for this year. Discuss one safety alert you found alarming.

ETHICS OF CLINICAL STUDIES

Many believe that 'informed consent' is all that is required to satisfy ethical concerns for clinical studies. It is far more complex than that. In addition to Informed consent, one must consider, Social and clinical value, Scientific validity, Fair subject selection, Favorable risk-benefit ratio, Independent review, and Respect for potential and enrolled subjects. https://clinicalcenter.nih.gov/recruit/ethics.html

The goal of clinical research is to develop generalizable knowledge that improves human health or increases understanding of human biology. People who participate in clinical research make it possible to secure that knowledge. The path to finding out if a new drug or treatment is safe or effective, for example, is to test it on patient volunteers. However, by placing some people at risk of harm for the good of others, clinical research has the potential to exploit patient volunteers. The purpose of ethical guidelines is both to protect patient volunteers and to preserve the integrity of the science.

The ethical guidelines in place today were primarily a response to past abuses, the most notorious of which in America was an experiment in Tuskegee, Alabama, in which treatment was withheld from 400 African American men with syphilis so that scientists could study the course of the disease. Various ethical guidelines were developed in the 20th century in response to such studies.

The Belmont Report. There are many guidelines in addition to rules and regulations that govern clinical study ethics. Some of the more influential ones include The Nuremberg Code (1947), Declaration of Helsinki (2000), Belmont Report (1979), CIOMS (2002) and US Common Rule (1991). Read the Belmont Report here: https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/index.html

Informed Consent. Any patient participating in a clinical study must do so under informed consent. Some exceptions to this rule include military operations or public health emergencies. Informed consent to the FDA does not just include patient authorization but an exchange of information between the subject and the individual obtaining this approval. The subject must have enough information about the study to make an informed decision about their participation in the study. Informed consent is outlined in the Informed Consent Form (ICF), allows the subject time to reflect, and has the information available to do so and therefore the ICF is submitted to the FDA for review.

Institutional Review Board (IRB). A company must also get approval from an Institutional Review Board (IRB) to perform human testing. *The IRB is a group responsible for protecting the rights, safety, and well-being of human subjects.* It is typically composed of a minimum of five, gender-diverse members; at least one science and one non-science member. The IRB general standards are covered and described in 21 CFR Part 56.

FDA has a comprehensive list of regulations that govern Clinical Studies here. International GCP guidance documents, which the FDA has collaborated, and links to other sites relevant to the conduct of clinical trials, both nationally and internationally are also found here.

Bioresearch Monitoring. The overarching goals of the FDA's bioresearch monitoring (BIMO) program are to protect the rights, safety, and welfare of subjects involved in FDA-regulated clinical trials; to determine the accuracy and reliability of clinical trial data submitted to FDA; and to assess compliance with FDA's regulations governing the conduct of clinical trials, including those for informed consent and ethical review. The BIMO program performs on-site inspections of both clinical and nonclinical studies performed to support research and marketing applications/submissions to the agency.

Beth is a 46-year-old post-menopausal mentally disabled woman with LCIS. LCIS is a disorder that means she is predisposed to develop breast cancer later in life. Her caregivers from her "home" with power of attorney for health care decisions bring her to the clinic for enrollment in STAR clinical trial, which is a randomized trial of tamoxifen v. raloxifene for the prevention of breast cancer in high-risk women. She fulfills all entry requirements but cannot consent due to her mental disability. The IRB is considering, is it ethical to permit Beth's power of attorney to enroll her in this study? *Remember, we are focusing on ethics here – not the law*.

1. What is an IRB? What is their function?

2. Using what you've learned in this chapter on GCPs, and the ethics resources below, argue for OR against the IRB ruling to grant Beth's power of attorney permission to enroll her in the study.

Office of Good Clinical Practice Mission Statement: *The Office of Good Clinical Practice is the focal point within FDA for Good Clinical Practice (GCP) and Human Subject Protection (HSP) issues arising in human research trials regulated by FDA.*

Clinical Study Initiation: The following is needed by a sponsor to initiate a clinical study:

- ✓ IRB
- ✓ Documentation of clinical investigator's credentials
- ✓ Financial disclosure (grant-sponsored etc.)
- ✓ GCP assurance statements
- ✓ Verification of study protocol training

Clinical Study Reporting: The investigator must provide clinical study progress reports at specified intervals during the study. Clinical Study Design: A clinical study is any research study that involves one or more human subjects testing experimental new drugs, devices or biologics (or control). It is the investigator's job to design the clinical study protocol. There are two main types of clinical trials; clinical (interventional) studies, and observational studies. For certain medical devices, accuracy studies may also be appropriate. Within the clinical study type, there are several subtypes, which may include placebo-control, double-blind studies, and randomization controls.

CLINICAL TRIALS

During a clinical trial participants may receive a particular intervention; an investigational new drug, device or biologic, or even psychological treatment, for example, diet or quit smoking. These interventions may be a comparison of a current drug to a new investigational drug, a placebo with no active ingredient to an existing drug, to name a few examples. The trial may also be randomized, placebo-control and blinded to reduce study bias. Clinical trials are commonly described by three phases (I, II, III). In Preclinical Studies the drug is tested on animals for safety and efficacy.

Phase I clinical trials primarily test for the safety of the proposed drug in healthy humans. During Phase I trials, the drug is administered to 20-80 healthy volunteers who will report any unexpected side effects and help establish the dosage levels that can be tolerated. In addition to evaluating the safety of the drug, its metabolic and pharmacologic properties in healthy humans are determined. If a drug meets the safety requirements at this phase and appears to have the desired impact of treatment, then it enters Phase II clinical trials.

Phase II trials are performed on a small number of patients to determine the drug's efficacy. Between 100 and 300 patients that the drug is intended to treat are given various dosages. Clinical trial participants are carefully monitored for side effects as well as the consequences of the drug treatment (or placebo). If no detrimental side effects are observed, and the drug seems to have some positive effect, it is ready to go to a broader Phase III study.

Phase III trials involve between 1,000 and 3,000 patients in double-blind studies usually conducted across several hospital sites. For most new drugs, these tests will last three or more years to establish the drug's benefits, recommended dosage, and long-term safety. Additional data on drug-drug interactions and risks versus benefits are collected.

Phase IV trials are performed after the drug has been approved by FDA. This post-market surveillance help gathers additional information on drug safety and efficacy by the general population.

MEDICAL DEVICE CLINICAL TRIALS

Not all medical devices undergo clinical trial testing. Minimal risk devices such as bandages (Class I) do not require clinical trials, where Class II devices of intermediate risk may depending on the device. Class III devices have a substantive risk and therefore undergo clinical trials. Another difference for medical device clinical trials is what is tested. For drugs, a dosage is tested, however, in devices the prototype is. Since there is an array of types of medical devices, we will further explore this in a later chapter focusing on medical devices.

The NIH has a public-accessible registry of all clinical trials currently underway and includes the results, appropriately named ClinicalTrials.gov.

Let's Explore!

Go to ClinicalTrials.gov and "search for a study" of something that interests you. For example, if you have been following the latest Ebola, or Zika virus outbreak you may wonder about the status of any current vaccine study. Write a 5-sentence summary of the study you selected.

CURRENT GOOD MANUFACTURING PRACTICES (CGMPS)

These guidelines for product manufacturing and testing represent a formal quality system that describes the general principles that must be observed during manufacturing. It is the company's responsibility to ensure GMP compliance and to do so efficiently and effectively. To this end, regulations are relatively flexible. *It is up to the manufacturer to establish design procedures, processing methods, and testing procedures.* This flexibility gives companies room to experiment and innovate.

Published in 1963, the first set of *Good Manufacturing Practices (GMP)* were intended to prevent deaths and injuries from contaminated products. These regulations seek to ensure quality and purity of drugs products from batch-to-batch and put a system in place to detect and reduce errors and variation in manufacturing. In 1990, FDA revised CGMP regulation to add the design controls authorized by *the Safe Medical Devices Act*. The FDA believed that it would be beneficial to the public and the medical device industry for the CGMP regulation to be consistent with international standards ISO 9001:1994 and ISO/CD 13485 *"Quality Systems--Medical Devices--Supplementary Requirements to ISO 9001."* After an extensive effort, the part 820 revision was published on October 7, 1996 (61 FR 52602) and went into effect June 1, 1997.

Additionally, it should be noted that *CGMPs represent only the currently accepted minimum standards for manufacturing, testing and packaging drugs and medical devices*. Most companies go beyond minimum guidelines to assure a customer a high-quality product. They frequently employ multiple quality systems, including voluntary ones, which gives the consumer peace of mind and a level of trust in the safety of the product.

GMP guidelines follow a few basic principles:

1. Define, control and validate all critical manufacturing processes.
2. Changes to the manufacturing process must be evaluated and approved.
3. Instructions and procedures must be clearly written and easy to understand.
4. Production operators must receive thorough training
5. The company must maintain accurate records demonstrating their adherence to guidelines and regulations.
6. Records must be comprehensive, complete and easily accessible.
7. In the case of pharmaceuticals, quality is not diminished in any way by the distribution process.
8. A recall system is in place so that any batch of a drug may be easily recalled from sale or supply.
9. The company responds to complaints, quality defects are investigated, and appropriate measures are taken to prevent future errors.

CGMP REGULATIONS. GMP regulations are included in Title 21 Chapter 1 of the CFR, in three regulations dealing with different types of manufactured products:

- for drugs (21 CFR 211)
- for medical devices (21 CFR 820)
- for blood and blood components (21 CFR 606)

The general principles of CGMP that all these regulations have in common:

- ✓ Quality, safety, and effectiveness are designed and built into the product, not tested or inspected into the product.
- ✓ Each step in the manufacturing process is documented and controlled to ensure the finished product meets design and compendia specifications.
- ✓ Process documentation provides evidence of compliance with CGMPs.

Three primary criteria used by FDA in the design of these CGMP regulations:

1. Regulations should contain objectives and not detailed specifications. They should allow latitude for different manufacturers to find their own means of compliance.
2. Regulations should contain requirements that are considered feasible and valuable as recognized and considered by experts as assuring quality.
3. If a practice can be established to be reasonable and relevant, then it can be a required practice even though it does not exist in the regulations.

Designing a GMP-compliant Process

The following is a brief summary on how to design a process:

1. The ***purpose*** of the process must be defined, that is, the desired output must be determined.
2. An ***endpoint***(s) that demonstrates the process is performed satisfactorily must be defined.
3. A method to ***measure the desired endpoint*** is required.
4. ***Raw materials*** and their specifications must be established.
5. The ***steps in the process*** must be determined, usually by experimentation.
6. The process must be ***scaled-up*** for production.
7. An ***analysis*** of potential problems must be performed, noting the "critical points."
8. ***Experiments*** must be carried out to determine how the process must operate at each critical point to make a quality product.
9. Methods to ***monitor*** the process must be developed.
10. Methods to ***control*** the process must be developed.
11. Adequate ***record-keeping*** procedures must be developed.
12. All ***SOPs*** required for the process must be written and approved.

CORRECTIVE ACTION PREVENTATIVE ACTION (CAPA)

CAPA is an important part of any CGMP design and focuses on the systematic investigation of root causes of issues in the manufacturing process. CAPA is a way in which manufacturers can implement continuous improvement plans and Quality Management systems and have a large impact on FDA compliance. There are three main CAPA categories: Corrective actions that have never occurred, Corrective Actions of re-occurrences, and Preventative Action to prevent an occurrence. CAPA is mandatory for medical device manufacturing, and we will discuss CAPA more in the medical device chapter. Learn more about CAPA here: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/Manufacturing/UCM334579.pdf

Setting standards for quality in the biotechnology industry is difficult due to the often new and complex manufacturing processes involved. How should the FDA set quality standards, for example, for chromatographic purification systems? These processes are difficult to validate and represent 'gray' areas where quality regulations are concerned. For this reason, companies frequently rely on regulations that the FDA has not yet finalized, and they comply voluntarily with CGMPs and Guidelines.

The CGMPs for Medical Device, Pharmaceuticals & Biologics will be further explored in those respective chapters. The commonality between the three products in CGMP regulations is that the regulations are intended to ensure the safety and efficacy of those products. Failure to abide by CGMP requirements may result in adulterated products and FDA enforcement repercussions (explored in a later chapter). As regulations change, manufacturers must learn and comply with the new regulations. *Continuous improvement, CAPA, internal audits and FDA inspections all work together to ensure Quality by Design, and not by testing.*

GOOD DOCUMENTATION PRACTICES (GDPs)

Regardless of the Guidance Practices being followed, they all exhibit the same philosophy of documentation practices, sometimes referred to as Good Documentation Practices (GDPs). The FDA uses the acronym *ALCOA (attributable, legible, contemporaneous, original and accurate)* to describe the importance of GDPs. The key to ALCOA is thorough documentation to ensure reproducibility and traceability.

The FDA's (and most quality system's) position regarding documentation is, 'if it isn't written down, it wasn't done.' Proper documentation is essential in a regulated company from discovery all the way through to the customer's hands. It provides regulatory bodies, lawyers, patent offices, and peer review publishers the information they need to validate the product's manufacturing process. While regulatory agencies tell you what you must do, they don't tell you how. *Current good manufacturing practices (CGMP), for example, is not a prescription for production manufacturing but guidelines*. This chapter focuses on some common and important elements of documentation that is found in both regulated and non-regulated workplace.

Documentation is a system of records, which serve three fundamental purposes:

- As a project-planning tool, documentation improves communication of project goals and priorities.
- Documentation provides a historical record of who-what-when-where-why-how; what was done, how it was done, what was changed, who did it, when it occurred, and why it was done. Accurate records are often a firm's best defense in cases of litigation.
- It is required by CGMP, ISO, QSR and GLP guidelines and regulations that clearly recognize that documentation makes good common sense.

The phrase *"documentation and traceability"* is familiar to all companies that must comply with FDA regulations. A company must be able to provide records to demonstrate traceability of all the parts of a finished product, including but not limited to raw materials, intermediates, and final lot batches. A final product can be released only if the documentation that has traced it from start to finish is complete, the product has met all required product specifications, and it has been produced in compliance with the necessary regulations. Therefore, *regulated companies have systems that ensure the work is recorded, that the appropriate documents are completed, and that the documents are stored in a secure and readily retrievable location*.

Documents that are archived must be easily retrieved in cases where customers question the quality of a product purchased, or when the company is being inspected or audited by a regulatory agency. In all cases, the consequences of missing documentation can be severe. Indeed, the company's very survival depends on these documents. Documentation is probably the first and most significant CGMP requirement needed in a new biotechnology company. The challenge is to establish, with limited resources and with a small staff who may have limited experience in CGMPs, the same degree of CGMP compliance as larger pharmaceutical companies.

In some companies, as a new product is developed for production, the process of record keeping is often viewed as inhibiting the progress of the project. Documentation slows down and burdens day-to-day operations due to the time spent filling out and signed off on forms and then carefully archiving them. There is no shortcut, however. Although cutting corners on record keeping may seem advantageous at first, lack of documentation can cause delays by causing fundamental experiments and processes to be needlessly repeated or result in faulty conclusions. *When a company manufactures a pharmaceutical, it produces two products: the drug and the enclosed documents that went into making the drug.*

In summary, documentation functions to: Record what has been done, establish ownership, provide workers specific instructions on how to perform a task, develop product specifications, demonstrate procedure was performed correctly, record experimental parameters, provide an evidence trail, ensures traceability, establishes a contract between a company and a consumer and establishes an agreement between a company and regulatory agencies.

TYPES OF DOCUMENTATION

Documentation is essential in all biotechnology work areas, although the specific types of documents and the systems for documentation vary according to the kind of workplace. Each company will have a set of documents to reflect their needs and requirements. There are three broad classes of documents.

- *Directive documents instruct employees how to perform a task.* Examples include standard operating procedures and protocols.
- *Data collection documents record data* to provide evidence that the directive document was performed and performed correctly.

- *Commitment documents lay out the organization's quality system;* goals and standards they commit to following. Mission statement, vision statement, and quality statements are all examples of commitment documents.

Laboratory notebooks: This documentation enables investigators to reconstruct their work, solve problems, detect mistakes, and prove to the scientific community that their results were properly obtained and were accurately reported. Laboratory notebooks can be used to establish a patent claim, assign credit for an original discovery, document data integrity for publication, and troubleshoot problems. It is, therefore, essential that it is written with indelible ink and be legible, clear and complete. Laboratory data can be subpoenaed in litigations. It can be examined by any regulatory agency that requests it. Notebook integrity is important even in non-regulated research labs.

A notebook may be used to document data to support research publications that have used government funding, may support a patent application, or may support an investigational new drug application or a new drug application to the FDA. A messy lab notebook, or one not maintained with integrity, may result in losing a patent, having grant funding withdrawn, having to repay grant funding, having to pay fines, losing your job and being given probation and jail time.

Let's Explore!

Read the following news article on the scientific misconduct of a Harvard scientist. What is Dr. Hauser accused? What are some of the 'mistakes' he made that he could have easily avoided? What are the ramifications he faces of being found guilty of scientific misconduct?
http://www.nytimes.com/2010/08/21/education/21harvard.html

Standard Operating Procedures (SOPs): People in production facilities use documents other than laboratory notebooks. Standard Operating Procedures (SOPs) that describe how to perform a particular task are essential in production facilities. *A procedure is a written document that provides a step-by-step outline of how a task is performed*. Most production facilities (and many laboratories) use procedures to instruct personnel how to perform particular procedures or tasks. Everyone follows the same procedures to assure that tasks are performed consistently and correctly. SOPs must be written so that they are clear, easy to follow, and can accommodate minor changes in instrumentation. *SOPs are typically written in command sentences rather than a narrative*. The placement and distribution of SOPs are controlled and documented, and they are reviewed on a periodic basis.

Standard Operating Procedures describe what is required to perform a task, what problems may arise and how to deal with them, how to document that the task was performed correctly and, lastly, who is qualified or responsible for the work.

SOPs are important for many reasons:

- ✓ Provide consistency each time a procedure or process is performed.
- ✓ Serve as reminders to ensure that work is done properly
- ✓ Used to train new employees the correct way to perform the work
- ✓ Reduce the possibility of failure by enabling the employee to complete any task

Forms: Forms are often associated with SOPs. These forms require an individual performing the task to monitor the process or procedure as it is being performed. *Filling in blanks and initialing the steps as they go along ensures that the steps are being followed correctly*. In production, the form often has blanks to record information about ID/lot numbers of raw materials, weights, times, temperatures, and other information necessary for quality control of the end product. In some production laboratories, a witness must sign key steps.

Protocols: *The term protocol may be used to refer to a procedure that will be performed one time* and may apply to a task or experiment that is intended to answer a question or test a hypothesis. The protocol outlines the steps that are to be followed in performing the experiment. SOPs are not intended to lead to the answer of a question or test a hypothesis. Protocols in research questions are addressed continuously. In production facilities, issues related to product performance, effects of storage (both short and long-term) on the product, quality of the product under different conditions, etc.

Reports: *A report is a formal document that describes the results of a completed task.* The report summarizes what was done, by whom, why, the data (results), and the conclusions. A report is written in a narrative addressed to a particular type of reader, with sufficient background information and technical information to achieve an appropriate amount of information. For example, reports to upper-level management may not include as many specific details as reports addressing regulators. Some reports are published in scientific journals, such as reports of basic scientific research. Other reports, such as those of investigations performed in a company, may or may not be published, but must be made available to inspectors.

Let's Explore!

Learn about the office of research integrity (ORI). What do they do? Go to: http://ori.hhs.gov/case_summary. Pick a case you find interesting and summarize the findings of the ORI and the punishment.

Lab reports and scientific papers have four typical functions:

- ✓ To persuade other people to accept your hypothesis based on the data you've presented.
- ✓ To publish your data, methods, material, and results for other researchers
- ✓ To become an accepted part of the scientific community by contributing to the body of knowledge
- ✓ To provide a record of research for documentation, storage, and future reference

Logbooks: Logbooks are used to maintain information about the status and maintenance of equipment or instruments. Logbooks are usually bound notebooks. Whenever an instrument or piece of equipment is used, calibrated, preventative maintenance performed and the instrument or item is repaired, that information is recorded in the notebook.

Analytical laboratory documents: Analytical laboratory documents contain data from analytical tests that measure some parameter in a sample. Clinical laboratories analyze blood for cellular components, ions, drugs and enzyme levels. The product is the test result. Documentation includes the sample being

tested and the test methodology. The elements of an analytical laboratory document differ from lab to lab and depend highly on regulations – such as CLIA (more on this in a later chapter!).

Numbering systems: Identification numbers are used to identify items uniquely. *Identification numbers are used for traceability purposes and are used for generalized inventory; raw materials, products, equipment, and even documents!* Identification numbers should identify the item uniquely.

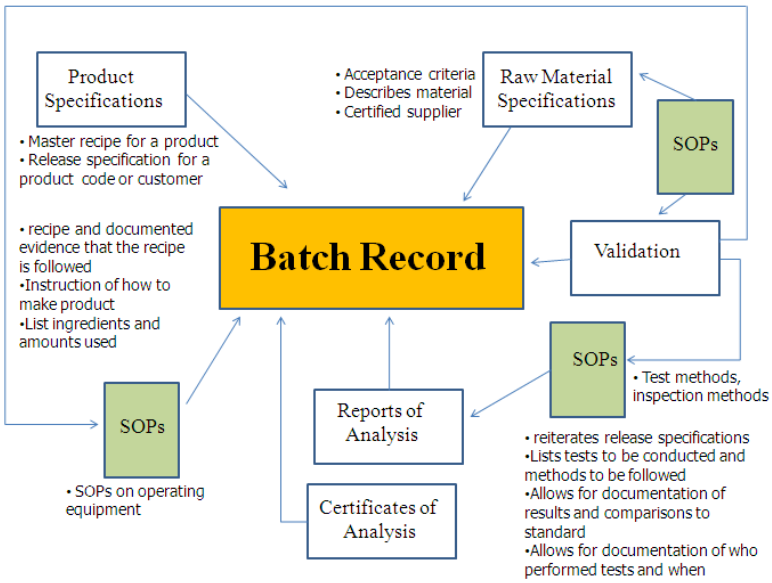
Labels: Labels identify instruments, raw materials, products or other items. Label format & contents are highly regulated by the FDA. *Can you find the CFR for labeling drugs?* _____

Chain of custody forms: Chain-of-custody is a term that refers to the maintenance of an unbroken record of possession of a sample from the time it is collected through delivery, receipt, storage, analysis, or disposition. Chain-of-custody documents are a method of organizing information about samples. The establishment of chain-of-custody procedures is necessary because the results of testing or analysis might be held as evidence in litigation proceedings. Each sample is assigned a unique identification number and logged in and out, as it is processed. To demonstrate the importance of chain of custody forms, consider, the O.J. Simpson trial verdict was based on inadequate documentation of the chain of custody of the DNA evidence. While the DNA fingerprinting science was sound and rigorous, poor documentation of who handled the blood samples, when, where, and how, led to the acquittal.

Training records: The FDA requires a documented continuous training program for compliance with the CGMP regulations. It is the responsibility of Quality Assurance to verify that a CGMP training program is implemented and that it is an ongoing program. In addition to CGMP training, regulations require that all employees be adequately trained in their job functions whether they are new hires or existing employees who are learning new methodologies or the operation of new equipment. Training is based on the company's own written and approved SOPs. It must be well documented and provides the necessary tools and expertise needed to train the employees.

Regulatory submissions: Regulatory submissions are documents designed to meet the requirements of an outside regulatory agency. Pharmaceutical companies must submit an application to the FDA showing their preliminary research on a drug, their plan for clinical trials and other relevant information before they can begin field-testing a new drug in humans.

Batch Records (Batch Production Records or BPR) are a requirement of Good Manufacturing Practices. They are an accurate copy of the corresponding Master Production and Control Record. BPRs must be carefully designed so that all appropriate process information is documented and demonstrated in writing. The BPRs must be reviewed for accuracy and must be signed and dated by a quality group before their use in manufacturing. A BPR is a combination of a SOP document and a form in that it directs operators in how to make the product and each step has blanks that are filled as the technician performs the action. For critical steps, a witness is required to watch and sign off on the BPR. Batch records are legal documents and are part of process validation compliance. The quality department officially issues the batch record to the production crew, and it is essential that blanks be filled in as procedures are performed. BPRs may be located in a central location or distributed in different areas provided that they are easily retrieved and filed in a logical and orderly manner. BPRs must be kept for a minimum of 1 year after the expiration date of a corresponding lot of the product.



Batch Record Contents

ELECTRONIC DOCUMENTATION

The biotechnology field uses a diverse and complex mixture of both paper and electronic documentation. There are many advantages and disadvantages to both, but companies tend to choose the documentation process that best serves their needs while meeting regulatory requirements. In response to the extensive use of electronic documentation and demand for systematic regulation of such documentation, in 1997 the FDA issued regulation 21 CFR Part 11 Electronic Signatures; Final Rule, to address these concerns. In 2003, the FDA released its final *"Guidance for Industry Part 11, Electronic Records; Electronic Signatures — Scope and Application".* https://www.fda.gov/regulatoryinformation/guidances/ucm125067.htm

The purpose of these regulations is to encourage pharmaceutical companies to adopt modern electronic documentation methods while requiring them to validate these electronic methods as secure, reliable and as searchable as paper documentation practices. The following table outlines some vocabulary used concerning 21 CFR Part 11.

21 CFR Part 11:

- Audit Trail. Computer generated time-stamp trail.
- Biometrics. Method to identify an individuals' identity.
- Closed System. Only accessible to people needing the system.
- Electronic Laboratory Notebook. Computer software programs designed for use as a lab notebook.
- Electronic Records. Text, graphics, data, audio information that is created, modified, maintained, archived, retrieved or distributed by a computer system.
- Electronic Signature. Equivalent to a hand-written signature.
- Encryption Software. Translates information into a secret code
- Hybrid System. Uses both systems; paper and electronic.
- Laboratory Information Management System (LIMS). Computer-based lab management system

Let's Explore!

Read the following article on unintentional scientific misconduct in using paper laboratory notebooks. From what you learned in this article, what are some examples of unintentional scientific misconduct? How can an electronic notebook help avoid some pitfalls of scientific misconduct using electronic notebooks?
http://socialscienceactivity.blogspot.com/2012/05/misbehaving-scientists-how-scientific.html

MANAGING CHANGE IN DOCUMENTATION

It is necessary for a production facility to follow the same procedures to the letter with each batch of product produced, and it is important that all supporting laboratory analyses also support a single set of protocols to reliably produce a consistent result. This rigid adherence to carefully described procedures helps prevent inconsistent results, but it stifles improvements that might help to improve or streamline a process. When a change is made, the change is carefully agreed upon by all parties involved, and all involved must have a procedure for enacting the change.

Typically, a request for changes to methods, sampling data sheets or calibration instructions may be made by anyone impacted by the proposed change. The request is made in writing following the company established Change Procedure. A committee or Quality Assurance Manager usually approves such a request depending on the hierarchal structure of the company, and the change being made. The Quality Assurance department is usually responsible for seeing that all copies of obsolete documents are electronically archived, and printed copies are removed and destroyed. They are also responsible for monitoring activity to ensure that approved changes are incorporated into the laboratory's routine work activity, and the change has had no known deleterious effects.

DOCUMENT STORAGE AND RETRIEVAL

It is crucial that all files relating to product manufacturing be kept securely and be readily accessed during quality system inspections (for example, by the FDA or ISO auditors). All records, when not in use, must be kept in locked (and fireproof) storage rooms. Computer data security will be maintained by data processing standard operating procedures for restricting entrance to computer data information.

How long records are kept is determined by regulations, the product made, and company policies. Records that are originated and maintained as hard copies are retained for five years, and three years after the batch has been released. Many companies have moved to transferring paper to electronic format after five years and kept indefinitely. Records generated by computer will be retained in that form indefinitely, with due care to keeping them in safe, hazard-free storage.

In summary, all materials received and used and all procedures and processes followed by a firm are carefully described and followed, leaving a paper trail that is carefully archived. However burdensome this might be to the company, it is essential in quality assurance and in protecting the firm from litigation. Furthermore, this paper trail is required by many regulatory agencies and is key to access international markets.

DOCUMENTATION REGULATIONS

Depending on the quality system used (and the regulations surrounding that quality system), there are many different types of quality system documentation requirements. Below is a very brief review of quality system regulations in the CGMP and ISO 9000 systems.

21 CFR 211: Title 21 Chapter 1 of the CFR contains all regulations concerning the safe production of food, drug, medical device, diagnostic, and biologic products for human and animal use under FDA supervision. (fda.gov) Documentation can be found under Part 211.

Let's Explore!

Go to the CFR database and search for Part 211. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm What subpart covers records? How long do records have to be maintained? Briefly, describe what each of the Records & Reports 8 sub-parts cover.

ISO 9001 DOCUMENTATION

A valid quality system, even a voluntary one such as ISO 9001, requires rigorous documentation and disciplined record keeping. Some of the activities of record-keeping required by ISO 9000 include, but may not be limited to training records, policies, procedures, instructions, protocols, purchasing records, test data, audit records, and calibration records. This type of documentation is part of the proof required to show that the company is following ISO guidelines in their quality management system and as such is a necessary component in maintaining their accreditation.

Documentation processes in an organization may differ depending on the size of the organization, the scope, and complexity of its activities and many other factors. But one thing is sure, for ISO 9001 certification this documentation must be thorough, complete and up-to-date. The ISO 9001:2015 guidance's on documentation allows an organization flexibility in the way it chooses to document its quality management system (QMS). ISO permits each company to determine what documentation is necessary to prove the effective planning, operation, and control of its processes, and continual improvement of the effectiveness of its QMS.

ISO 9001:2015 clause 4.4 Quality management systems and its processes require an organization to "maintain documented information to the extent necessary to support the operation of processes and retain documented information to the extent necessary to have confidence that the processes are carried out as planned." (ISO, 2015). Guidance on the requirement for documented information for ISO can be found here: http://www.iso.org/iso/documented_information.pdf

As the Quality Manager of Proteins 'R Us, you are in charge of a pharmaceutical firm's Quality Department and have been given notice by a customer's lawyer that his client has suffered severe damage from your antibiotic product and intended to sue for damages. Explain in what way each of the following documents could play a role in protecting your firm from this litigation:

a. R & D laboratory notebooks
b. Monthly reports from R & D to upper-level management
c. Production equipment logbooks
d. Product label
e. Chain-of-custody forms
f. Production personnel training records
g. BPRs

Summary

- ✓ Guidance documents (and guidelines) are used to relate the FDA current regulatory principles and practices for the manufacturing of products.
- ✓ All non-clinical safety studies on animals of new drugs, drug biologics, veterinary drugs, and some food additives fall under the purview of GLP regulations.
- ✓ GCPs apply to the performance of clinical trials of drug safety and efficacy in human subjects.
- ✓ Any patient participating in clinical studies must have informed consent. The IRB is responsible for the rights, safety, and well-being of human subjects by reviewing clinical study protocols.
- ✓ The overarching goals of the BIMO program is to protect the rights, safety, and welfare of human subjects by conducting on-site inspections
- ✓ CGMP are guidelines for product manufacturing
- ✓ CAPA focuses on the systematic investigation of the root-cause of issues in the manufacturing process

CHAPTER 6: THE DRUG APPROVAL PROCESS

Objectives

- ✓ Difference between the terms: pharmaceutical, biopharmaceutical, biologic, generic, biosimilar, and drug.
- ✓ Identify the significant milestones in manufacturing a drug; R&D, pre-clinical studies, clinical studies and the application process for new products, & post-market surveillance.
- ✓ Differentiate between the different drug application review processes: NDA, ANDA, BLA, fast track, OTC, priority, and orphan.
- ✓ Explore exceptions to the drug review & patent process.
- ✓ Utilize FDA databases to look up drugs; orange book, clinical trials, drug database
- ✓ Demonstrate knowledge of Prescription drug labeling and explain limitations to drug advertising

INTRODUCTION – THE PHARMACEUTICAL PRODUCT APPROVAL PROCESS

This chapter provides an in-depth exploration of the regulations and submission requirements for a new drug. The process of bringing a drug out of development and onto the market is very rigorous, time-consuming and expensive. By some estimates, the process can take upwards of 15 years, and a typical drug company may spend close to $800 million to create a marketable new drug. The biggest hurdle a new drug must overcome is the testing required by the FDA. As previously discussed, prescription drugs are regulated under the Federal Food, Drug, and Cosmetic Act of 1938 (FD&C Act). Only about 1 in 5000 potential drugs successfully pass through the testing process to be approved by the FDA for patient use. The FDA has an extensive website outlining the drug development process.
https://www.fda.gov/Drugs/DevelopmentApprovalProcess/default.htm

Before we begin diving into the regulation, it's important to understand standard pharmaceutical manufacturing terminology. Here are some relevant key terms.

- A pharmaceutical product is a chemical agent that acts on the body to create a therapeutic effect. A therapeutic effect may include the treatment or prevention of symptoms of illnesses, injuries or disorders in humans and animals.
- The term drug applies to pharmaceuticals used in the diagnosis, cure, treatment, and prevention of disease and is substances, which are recognized by an official pharmacopeia or formulary. A new drug refers to drugs which the safety and effectiveness of an application are not previously known.
- A generic drug is the same as a brand-name drug in dosage, safety, strength, how it is taken, quality, performance, and intended use. A generic drug must contain the identical amounts of the same active ingredient(s) as the brand name product. The generic drug product must have an equal therapeutic effect as the brand-name drug.
- A New Molecular Entity (NME) is an active ingredient that has never been marketed in the United States in any form.
- A therapeutic biological product is a protein derived from living material that can be used to treat or cure diseases, such as cells or tissues.
- A biopharmaceutical is a specific type of drug created via genetic engineering of a particular organism. The term 'biopharmaceutical agent' is synonymous with this kind of drug.
- A biosimilar is a biological product, which is 'biosimilar' to an FDA-licensed biological product (e.g., Biopharmaceutical, biologic, vaccine, proteins, tissues).
- A medical device definition is complicated. A medical device can range from a tongue depressor to a clinical testing kit, to a replacement hip. Due to the specialized complexity of devices and combination applications (for example birth control implants), we will address device regulation in a later chapter.

CDER. *The branch of the FDA that oversees drugs is the Center for Drug Evaluation and Research (CDER).* This FDA Center evaluates a drug for both safety and effectiveness. It's important to note that they do not test the drug themselves but reviews the evidence the company sends them to ensure the drugs are safe and effective. The CDER team is constructed of physicians, chemists, pharmacologists and other scientists.

OVERVIEW OF THE DRUG DEVELOPMENT PROCESS

The long life cycle of drugs can take upwards of 12 years and costs millions of dollars:

1. Development.
2. Pre-Clinical Testing
3. IND
4. Clinical Testing
5. NDA
6. Approval process.
7. Marketing.
8. Post-release surveillance.

Let's Explore!

The FDA provides a simple overview of the drug review process here.
https://www.fda.gov/drugs/resourcesforyou/consumers/ucm143534.htm
Do over-the-counter medications go through the same approval process?

The first milestone for any new drug occurs during the research and discovery phase. Some form of experimentation in an R&D lab leads to the development of an active pharmaceutical ingredient (API) that may have therapeutic activity in the human body. If the active ingredient is believed to have real potential, the drug moves into the development stage. This early stage of development involves what is known as "preclinical testing," and is carried out in laboratories and animal testing facilities. This preclinical phase must be successful before testing can happen in humans. If the drug performs well during this stage, the company can file an Investigational New Drug Application (IND) with the FDA to request permission to begin testing on human subjects.

There are three major phases a drug must pass through during human subject testing (clinical studies). If the drug passes through clinical studies successfully, the company can then submit a New Drug Application (NDA) to the FDA. If the FDA grants its approval, the company can finally begin selling the product, but its involvement does not end there. The FDA will continue to interact with the company to help ensure that the product is manufactured safely.

It is important to note that the company that sponsors the drug development may not be the company performing the tasks of the development. Contract Research Organizations (CROs) are frequently enlisted and paid to perform specific tasks of the drug development. These tasks may include animal testing, human testing, and actual manufacturing.

MILESTONES IN THE MANUFACTURE OF A DRUG

RESEARCH & DEVELOPMENT. The earliest approaches to drug discovery involved identifying and isolating the active components of naturally occurring chemicals, such as those found in plants and other homeopathic remedies. In the modern laboratory, researchers also search for the causative agents of diseases (e.g., missing or over-active proteins) to guide drug research by understanding what problems must be targeted. High Throughput Screening (HTS) is another approach, which enables scientists to screen thousands of potential drugs all at once and allows for quick identification and targeting of potentially useful compounds.

	Preclinical Testing		Phase I	Phase II	Phase III		FDA		Phase IV
Years	3.5		1	2	3		2.5	12 Total	
Test Population	Laboratory and animal studies	File IND at FDA	20 to 80 healthy volunteers	100 to 300 patient volunteers	1000 to 3000 patient volunteers	File NDA at FDA	Review process / Approval		Additional Post marketing testing required by FDA
Purpose	Assess safety and biological activity		Determine safety and dosage	Evaluate effectiveness, look for side effects	Verify effectiveness, monitor adverse reactions from long-term use				
Success Rate	5,000 compounds evaluated		5 enter trials				1 approved		

FDA oversight of drug approval process

PRECLINICAL DEVELOPMENT. Before testing a drug in humans, it must undergo nonclinical testing to obtain basic toxicity and pharmacological data the FDA requires before safety testing in humans (Phase I). This stage can take anywhere from 1-4 years which may not include filing the IND which is needed by the FDA to pursue clinical studies in human subjects. The FDA may require further testing it sometimes allows to be in conjunction (or in parallel) with clinical studies.

The objectives of preclinical development are:

- ✓ Identifying the physical and chemical properties of the candidate drug.
- ✓ Testing the candidate drug in vitro.
- ✓ Determining formulation for administration to test subjects and patients.
- ✓ Developing manufacturing methods for the candidate drug.
- ✓ Testing the candidate drug in cultured cells.
- ✓ Testing the candidate drug in animals for safety.
- ✓ Developing analytical assays.
- ✓ Securing intellectual property protection for the potential product, its uses, and its manufacture.

For this potential drug to be useful, it must be, stable, safe, and be manufactured in a practical way. This stage is also dedicated to determining the drug's activity, chemical attributes, and solubility and outlining manufacturing schemes to ensure its potential as a drug. If the drug shows potential in the laboratory, the next step requires toxicity tests. *These tests are also known as ADME studies. ADME stands for Absorption, Dissemination, Metabolic and Excretion.*

These ADME studies are carried out on animals and also help researchers determine the following about the drug' characteristics:

- How much of the drug is absorbed by the blood?
- How the substance is metabolically altered in the body.
- What are the toxicity effects of metabolic by-products?
- How quickly will the drug and its by-products be excreted?

Toxicity. Safety assessment is done using toxicity studies. These studies are conducting using GLP guidelines for 30-90 days, in a minimum of two mammalian species, one of which must be non-rodent. The dosage, length of study and complexity of study is related to the proposed clinical study; duration and complexity should be equal to or exceed what is proposed in humans. Additionally, if the new drug is also a

New Chemical Entity (NCE) and has no long-term human data at all, the study may be required to exceed 12 months.

Reproductive Toxicity. Fertility and embryonic development are also studied extensively in human clinical trials. This includes early embryonic development, embryo-fetal development, as well as pre and post-natal development.

Genotoxicity. Genotoxicity, the propensity to damage genetic information, is also extensively studied in both *in-vitro* and *in vivo*. This assessment of mutagenicity is tested in both bacteria and mammalian cells.

Carcinogenicity. Carcinogenicity studies are not required before clinical studies begin and may not have to be done for some products. These studies may take upwards of 2 years to complete.

INVESTIGATIONAL NEW DRUG APPLICATION (IND). If the drug candidate is promising in the preclinical testing, then the company compiles its data and submits a plan to test the drug on human subjects to the FDA, called the Investigational New Drug Application (IND). *The IND contains information from the animal studies, information relating to the composition and manufacture of the drug and the investigational plan.* The IND application includes a description of the product, the results of animal tests, and the plans for further testing. The FDA then decides whether the company's materials are sufficiently complete that the company can begin testing the product in humans.

The IND is not 'approved' rather it becomes active within 30 days of the FDA receiving it. If deficiencies are discovered, the company is given an opportunity to correct it. If the issues are not addressed, the FDA will put the clinical studies on hold until they are. Some areas of concern for the FDA include unreasonable risk to human health, investigators without the appropriate credentials, and incomplete (or misleading) preclinical data.

IND Amendments. During the clinical development, the IND must be updated if any changes are made. These amendments may include changes to protocols, new toxicology data from animal studies that extended into the clinical studies, any adverse events, and any new findings that reveal this drug may cause a significant health risk for human volunteers.

CLINICAL DEVELOPMENT. The government has an interest in protecting the public from defective products and drugs. Therefore, companies must demonstrate their effectiveness and safety before mass distribution. However, the only way they can actively do this is by actually having human subjects test out their products. As a refresher from the previous chapter on clinical studies, watch this video on clinical trials: https://www.youtube.com/watch?v=pm1igf85u0A

TEST YOUR KNOWLEDGE!

Case Study: Drug Development: "from Fish to Pharmacies: a Story of Drug Development."
https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/default.htm

1. After obtaining promising research in the lab, what did the drug developers do next before being permitted to perform their clinical trials?

2. In your own words, explain what 'clinical trials' are. Include the three stages of clinical trials.

3. What 'practices' govern clinical trials?
http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/default.htm

4. When the clinical trials are completed, what is the next step to getting the drug approved?

Clinical Trials Data Bank. As previously discussed all clinical data is published in the clinical trials data bank at clinicaltrials.gov, which is maintained by the National Institutes of Health (NIH). Companies are required to submit their Phase 2 and 3 clinical data. A company may request to withhold this data if they can prove that it will interfere substantially with a timely clinical study, however, this is up to the FDA.

NEW DRUG APPLICATION (NDA) if the drug passes all three phases of testing. The application data must show convincing evidence that the new drug or biologic is safe, reliable and effective for the indications on the labeling. The FDA employs expert reviewers who examine the test results and determine whether the new drug can be approved.

There are several types of drug applications:

- Traditional 505(b)(1) NDA – *FD&C Act*, Section 505(b)(1)
- 505(b)(2) NDA
- Abbreviated NDA (ANDA) 505(j)
- Original BLA – *PHS Act*, Section 351(a) – for biologics discussed in next chapter
- Biosimilar BLA – *PHS Act*, Section 351(k) – for biosimilars discussed in next chapter

NEW APPLICATION OF THE SAME DRUG – REVIEW PROCESS

Approval of new application of the same drug: If a company wants to expand the use of their drug to a new application, previous safety studies are usually still applicable; however, new clinical studies will be required to test the efficacy of the drug for its new application. The 505(b) (1) NDA is the complete application with all the appropriate study information outlined in the CFR that will demonstrate the drug's safety and effectiveness. The 505(b) (2) NDA can include drugs where safety and effectiveness have been established in previous studies (by other companies) allowing companies to develop treatments quicker with less clinical study volunteers. An example of an application would be instead of a ten-day treatment of the drug, the drug now has a slow-release capsule, so it has only 3-day treatment, but is slowly released over ten days.

GENERIC DRUG REVIEW PROCESS.

Interestingly, the term 'generic drug' is not defined in FDA regulations. A generic drug must have the same active ingredient, same potency, and the same dosage to be sold without having to repeat the extensive clinical trials used in the development of the original, brand-name drugs. Generics must deliver the same amount of active ingredient into a patient's bloodstream over the same period as the brand name – this is referred to as bioequivalence. *The rate and extent of absorption of a drug are called its bioavailability*. If the bioavailability of the two is similar, the drugs are bioequivalent.

ABBREVIATED NEW DRUG APPLICATION (ANDA).

An ANDA is an application for approval for a generic drug product. This application contains data submitted to FDA's Center for Drug Evaluation and Research, Office of Generic Drugs for their review for approval. Generic drug applications are called "abbreviated" because they frequently are not required to include any preclinical (animal) or clinical (human) data to show efficacy and safety. Instead, *a generic applicant must scientifically demonstrate that its product has therapeutic equivalence*. Therapeutic Equivalence means the drug must have the same clinical effect and safety (under the same labeling) as the non-generic drug and must have the identical active ingredient, with identical strength, quality, purity, and potency. Although it does not need to have the same inactive ingredients. Once approved, the company can then manufacture and market the generic drug product to provide a low-cost alternative to the brand-name drug.

BIOLOGIC LICENSE APPLICATION (BLA).

A BLA is required for biological products submitted to CBER or CDER (characterized protein). The BLA must include all safety and efficacy information necessary for drug approval. A 351(a) application – Original BLA – contains all the information required and outlined in 21 CFR 601.2. A 351(k) application is an abbreviated BLA for a biosimilar. Although some biologics are overseen by CDER, the BLA process is further explored in the Biologics Regulatory Approval chapter.

OVER-THE-COUNTER (OTC) DRUG REVIEW PROCESS

Over-the-counter (OTC) drugs are drugs, which can be obtained and used without a prescription. More than 300,000 OTC drug products are available in the US. OTC drugs are considered safe - their benefits outweigh the risks, they have minimal potential for abuse, consumers can use them for self-diagnosed applications and therefore a healthcare professional is not needed to oversee their safe and effective use.

It is noted, although OTC drugs are available without a prescription, they still can carry risks, in particular, risks of side effects or overdose. A typical example is Tylenol (active ingredient acetaminophen), which most people assume is very safe. However, an overdose of this OTC drug results in over 44,000 individuals in the emergency room and over 400 die each year of liver failure. Learn more here!
https://www.sciencedaily.com/releases/2015/06/150622124713.htm

Some OTC drugs are technically kept 'behind the counter' such as emergency contraceptive, and pseudoephedrine. The pharmacist will dispense with age and application verification.
Although many drugs are approved for OTC use through the new drug review process, other OTC medicines are regulated under the OTC drug review process. This process relies on published monographs, which outline acceptable ingredients, doses, formulations and consumer labeling for OTC drugs. Products that conform to a final monograph may be marketed without prior FDA clearance.

NEW DRUG REVIEW PROCESS - SUMMARY

https://www.fda.gov/forpatients/approvals/fast/ucm20041766.htm

- Priority reviews. These products represent significant improvements compared with marketed products.
- Standard reviews. These products have therapeutic qualities similar to those of already marketed products.
- Orphan drugs. The FDA administers a program that provides incentives to develop drugs for use in patient populations of 200,000 or fewer. These are referred to as 'rare diseases.' To learn more about rare diseases, see the Office of Rare Diseases Research: http://rarediseases.info.nih.gov/. Companies manufacturing orphan drugs receive the following inducements: seven-year marketing exclusivity, tax credit for the product-associated clinical research, research design assistance from FDA and grants.
- Accelerated approval. This program makes products for serious or life-threatening diseases available earlier in the development process by relying on an effect on a surrogate endpoint to predict clinical benefit.

- Fast-track development. Fast track is a process designed to facilitate the development, and expedite the review of drugs to treat serious conditions and fill an unmet medical need.
- Tentative approval. This program is issued to the drug company when the application is approvable before the expiration of any patents or exclusivities accorded to the reference listed drug product.
- Breakthrough Therapy Designation. When drugs show substantial promise in early clinical trials for a severe, life-threatening disease, the company may request a breakthrough therapy designation which permits it the same benefits as a fast-track designation.

SPECIAL DRUG INCENTIVE PROGRAM

There are several sponsored programs to encourage the development of a drug that is in demand. The *Orphan Drug Act* and GAIN (Generating Antibiotic Incentives Now) and Presidential Emergency Plan for AIDS Relief (PEPFAR) are three examples of special drug incentive programs available. GAIN is an incentive program to develop drugs that treat life-threatening bacterial infections. GAIN drugs get Fast Track and Priority review in addition to 5-year market exclusivity (7 yr for orphan drugs!). To learn more about the *FDA Safety and Innovation Act* *https://www.fda.gov/RegulatoryInformation/LawsEnforcedbyFDA/SignificantAmendmentstotheFDCAct/FDASIA/ucm20027187.htm*

The FDA does permit the approval of drugs and vaccines intended to counter biological, chemical, and nuclear terrorism without first proving their safety and worth in Phase II and III trials. Clearly, it would be unethical to deliberately expose humans to harmful radiation or pathogens to test the effectiveness of treatment. For example, the FDA expedited approval of one new drug, Cipro®, an antibiotic that adequately treats those who are exposed to anthrax. The FDA also has a more streamlined process for approval of "orphan drugs" (drugs with small numbers of beneficiaries but with great benefit).

POST-MARKETING SURVEILLANCE

The drug can be manufactured, marketed and sold once it has been approved. Manufacturing must follow current Good Manufacturing Practices (CGMP), to ensure the quality of the product. Post-marketing surveillance is used to determine the drug's long-term safety. Data is collected from patients and doctors. Adverse reactions are reported to the FDA. Extreme cases of adverse reactions can cause a drug to be withdrawn from the market. The FDA checks for regulatory compliance by performing periodic inspections of production facilities (announced or unannounced) and by testing material samples either provided by the pharmaceutical company or acquired through retail channels.

PATENTS AND EXCLUSIVITY

Brand-name drug manufacturers have patent exclusivity for 20 years in the US. However, some drugs may qualify for patent & non-patent exclusivities, which can delay the market application of a generic drug. Drug patents are a complex issue in the US due to this specifically. Patent term extension can be given for exclusivity with antibiotic drugs, orphan drugs, pediatric drugs to name a few.

THE ORANGE BOOK – excerpt from the FDA Website:

*"The publication, **Approved Drug Products with Therapeutic Equivalence Evaluations** (the List, commonly known as the Orange Book), identifies drug products approved for safety and effectiveness by the Food and Drug Administration (FDA) under the Federal Food, Drug, and Cosmetic Act (the Act). Drugs on the market approved only by safety (covered by the ongoing Drug Efficacy Study Implementation [DESI] review [e.g., Donnatal® Tablets and Librax® Capsules] or pre-1938 drugs [e.g., Phenobarbital Tablets]) are not included in this publication. Read more… https://www.fda.gov/Drugs/InformationOnDrugs/ucm129662.htm."* (FDA, 2016).

Let's Explore!

Go to The Orange Book and search for any drug you currently use:
https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm

PRESCRIPTION DRUG LABELING & ADVERTISING

The FDA also has authority over labeling and marketing of drugs. Labeling here is not only what is written on the container but any material associated with the product, including package inserts, Medication Guides, marketing material (direct to consumer and promotional) even social media!

21 CFR 201.56 & 21 CFR 201.57

Guidance for Industry: Labeling for Human Prescription Drug and Biological Products

There are specific requirements of labeling outlined in 21 CFR 201 some of which include appropriate placement and prominence of words on the label. All labeling, advertising, and promotional material must be submitted to the FDA for review before product approval. Here is a summary of a few of the guidance documents regarding labeling.

21 CFR 201.57(c)(1)	Boxed Warnings & Precautions
21 CFR 201.57(c)(2)	Indications & Usage
21 CFR 201.57(c)(3)	Dosage & Administration
21 CFR 201.57(c)(4)	Dosage forms & Strength
21 CFR 201.57(c)(6)	Warnings
21 CFR 201.57(c)(7)	Adverse Reactions
21 CFR 201.57(c)(8)	Drug Interactions
21 CFR 201.57(c)(10)	Drug Abuse & Dependence
21 CFR 201.57(c)(11)	Over dosage
21 CFR 201.57(c)(17)	Storage and handling

CDERLearn. https://www.fda.gov/training/forhealthprofessionals/default.htm CDERLearn is an FDA website for training regulatory affairs professionals about drug approval. There are over ten chapters targeting specific areas of drug development. Quite a few significant ones can be found at CDERworld. https://www.accessdata.fda.gov/scripts/cderworld/

Let's Explore!

a. Decide on a drug that has an effect on your life (positive or negative). Why did you choose this drug?

b. Look up your drug on the FDA database and write a one-paragraph summary including its name, who makes it and what it is used for. NDA APPLICATION NUMBER: _____
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

c. Look up your drug's clinical studies – be sure you get the clinical study for the approved indication! Use the NDA Application number in the search bar. https://clinicaltrials.gov/

d. Look up the dates of when your drug was approved, and its patent expire date. Search by Application number! http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm

e. Any other database you've to use this semester you can look up your drug? Can you find the actual NDA application on the website?

Summary

- ✓ The process of bringing a drug out of development and onto the market is a rigorous, time-consuming and expensive endeavor taking upwards of 15 years and millions of dollars
- ✓ CDER is the center that oversees drug approval
- ✓ If a drug is promising in pre-clinical studies, the company must submit an IND to test the drug on human subjects
- ✓ If a drug passes all phases of clinical studies a company may submit an NDA to market the drug
- ✓ An Abbreviated NDA (ANDA) is used for generic drug application and the drug may not need pre-clinical and clinical studies – but must demonstrate therapeutic equivalence
- ✓ A BLA is used on biologic (Drugs in CDER) for therapeutic proteins
- ✓ Over-the-counter drugs that do not need a prescription can still pose considerable risks to consumers and therefore are highly regulated.
- ✓ There are alternative review processes such as Fast-track, Orphan Drug, Priority Review, Breakthrough Designation that all provide a faster approval route in exceptional circumstances

CHAPTER 7: THE REGULATION OF BIOLOGICS

OBJECTIVES

- ✓ Understand what is a biological therapeutic product
- ✓ Explore the complicated approval process for biologics
- ✓ Demonstrate understanding of the different product categories CBER has regulatory authority
- ✓ Distinguish between a drug, biologic, generic drug, reference product, and biosimilar

Biologics are revolutionizing the biotechnology and health sector – and the most important biotechnology products of this century. Biologics include vaccines, tissue transplants, gene therapy & stem cell treatment and may include biological molecules such as proteins, and nucleic acids, living tissues, and cells.

The official definition for a biologic – or a therapeutic biological product - is *"any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product"* (Public Health Services Act, 1944). Some biologics treat a disease or disorder, and some diagnose or prevent them. According to the Public Health Services Act (*PHS Act*) Section 351 (a) to manufacture and sell a biologic in the US, you must apply and receive a Biologics License (BLA). Since some biologics are considered drugs, they must comply with the *FD&C Act* Title 21 of the CFR pts 210 and 211 for CGMP and may be overseen by CDER!

HISTORY OF BIOLOGICS REGULATION

In 1902, the 57th United States Congress passed the *Biologics Control Act* in response to the death of children from contaminated vaccines in two separate incidences. This Act set a precedent *to "regulate the sale of viruses, serums, toxins, and analogous products in the District of Columbia; to regulate interstate traffic in said articles, and for other purposes*, and mandated producers of vaccines be licensed annually for the manufacture and sale of antitoxins, serum, and vaccines" (fda.gov).
https://history.nih.gov/exhibits/history/docs/page_03.html

In 1930 the National Institutes of Health was born and in 1937 created the Division of Biologics Control. It was not until 1972 that this division was transferred to the FDA and renamed the Bureau of Biologics, and in 1988, was moved to the Center for Biologics, Evaluation & Research (CBER). CBER's regulatory authority is derived from Section 351(a) of the *PHS Act* of 1944, which required Product License Applications.

As you have probably noticed the definition of drug and biologic overlap and have resulted in confusion about which Center would oversee biologics that act like drugs. The FDA's stated policy is to review each product on a case-by-case basis to determine the Center of oversight, which is usually based on the drug's *Primary Mode of Action (PMoA).* In 1991, CBER & CDER executed an Intercenter Agreement (ICA) to attempt to clarify the regulation of biologics by outlining which of the Centers should regulate which products. They also clarified combination products in this agreement. Further, in 2003, the FDA transferred some of the therapeutic biological products (well-characterized proteins) from CBER to CDER hoping to strengthen the product divisions.
https://www.fda.gov/CombinationProducts/JurisdictionalInformation/ucm121179.htm

In 2009, the *Biologics Price Competition and Innovation Act* (*BPCI Act*) created an abbreviated approval pathway for *biosimilars*. Moreover, in 2014 the FDA released a new draft guidance on market exclusivity for biological products approved under 351(a) of the *PHS Act*.

Depending on the regulatory pathway, a product may have differing premarket submission channels. It is important for a company to quickly establish the path to take since it affects not only the final approval, but approval on every step of the process including pre-clinical, and clinical studies. Depending on the assigned

Center the product may require a BLA or NDA, and in the case of some combination products, a PMA. More on approvals later in this chapter. The FDA has a review process to help clarify confusion, called the Request for Designation Process (RFD). The RFD helps establish a formal designation of which Center will oversee the regulatory process for combination products or for products where there is no clear jurisdiction. Jurisdictional updates are posted to the FDA website.

CBER OFFICES & DIVISIONS

The Center for Biologics, Evaluation & Research (CBER) is the primary Center in the FDA, which oversees the regulation of biologic & related products. We will explore in this chapter the broad range of biological products CBER reviews. There are three main review offices in CBER; Office of Blood Research and Review (OBRR); Office of Cellular, Tissue and Gene Therapies (OCTGT); and the Office of Vaccine Research and Review (OVRR). It is important to note here that CBER does oversee medical devices that are associated with the collection and testing of licensed blood and cellular products. CBER states their mission *"To ensure the safety, purity, potency, and effectiveness of biological products including vaccines, blood and blood products, and cells, tissues, and gene therapies for the prevention, diagnosis, and treatment of human diseases, conditions, or injury. Through our mission, we also help to defend the public against the threats of emerging infectious diseases and bioterrorism."* (FDA, 2016)

Biologics Product Categories (from the FDA):

- Allergenics are allergen extracts, allergen patch tests, and antigen skin tests
- Blood & Blood Products Blood, Blood Components, Blood Bank Devices, Blood Donor Screening Tests
- Cellular & Gene Therapy Products Gene-based Treatments, Cell-based Treatments, Cloning
- Tissue & Tissue Products Bone, Skin, Corneas, Ligaments, Tendons, Stem Cells, Sperm, Heart Valves
- Vaccines for Use in Children and Adults, Tuberculin Testing
- Xenotransplantation Transplantation of Non-Human Cells, Tissues or Organs Into a Human

Allergenics. "**Allergen extracts** are used for the diagnosis and treatment of allergic diseases. This may include general seasonal allergies such as hay fever, or more severe allergies such as bee venom or food allergy. Currently, there are two types of licensed allergen extracts; injectable extracts and sublingual extract tablets. You are probably most familiar with injectable allergen extracts that are used for both diagnosing allergies as well as treating them. These extracts are manufactured from natural substances such as insect venom, animal hair protein, and pollens. Sublingual allergen extract tables are used for treatment only of allergic reactions. **Allergen Patch tests** are diagnostic tests applied to the surface of the skin by healthcare providers to determine the particular cause of contact dermatitis. **Antigen skin tests** are diagnostic tests injected into the skin to aid in the diagnosis of infection with certain pathogens" (fda.gov).

Blood & Blood Products. "CBER regulates the collection of blood and blood components used for transfusion or the manufacture of pharmaceuticals derived from blood and blood components, such as clotting factors, and establishes standards for the products themselves. CBER also regulates related products such as cell separation devices, blood collection containers and HIV screening tests that are used to prepare blood products or to ensure the safety of the blood supply. CBER develops and enforces quality standards, inspects blood establishments and monitors reports of errors, accidents and adverse clinical events" (fda.gov).

Cellular & Gene Therapy Products. "CBER regulates cellular therapy products, human gene therapy products, and certain devices related to cell and gene therapy. Cellular therapy products include cellular immunotherapies, which includes both adult and embryonic stem cells. Human gene therapy refers to products that introduce genetic material into a person's DNA to replace faulty or missing genetic material, thus treating a disease or abnormal medical condition. Although some cellular therapy products have been approved, *CBER has not yet approved any human gene therapy product for sale*" (fda.gov).

Let's Explore!

To learn more about how the FDA regulates Gene Therapy products, watch the following video.
http://fda.yorkcast.com/webcast/Play/d8d4e70c6f1b4b7aa1c697580300089ef1d
What regulations must companies follow for Gene Therapy products?

Tissue & Tissue Products. "Human cells or tissue intended for implantation, transplantation, infusion, or transfer into a human recipient is regulated as a human cell, tissue, and cellular and tissue-based product under 21 CFR Parts 1270 and 1271. Parts 1270 and 1271 require tissue establishments to screen and test donors, to prepare and follow written procedures for the prevention of the spread of communicable disease, and to maintain records. FDA has published three final rules to prevent the introduction, transmission, and spread of communicable disease; one final rule requires firms to register and list their HCT/Ps with FDA; the second rule requires tissue establishments to evaluate donors for infectious diseases; and the third final rule establishes current good tissue practices for HCT/Ps. It's important to note here that *CBER does not regulate the transplantation of human organ transplants such as liver, kidney, or heart" (fda.gov)*

Vaccines. "Vaccines, as with all products regulated by FDA, undergo a rigorous review of laboratory and clinical data to ensure the safety, efficacy, purity, and potency of these products. Vaccines approved for marketing may also be required to undergo additional studies to further evaluate the vaccine and often to address specific questions about the vaccine's safety, effectiveness or possible side effects. According to the Centers for Disease Control and Prevention, vaccines have reduced preventable infectious diseases to an all-time low, and now few people experience the devastating effects of measles, pertussis, and other illnesses. Many of these are childhood vaccines that have contributed to a significant reduction of vaccine-preventable diseases" (fda.gov)

Xenotransplantation. According to the FDA, xenotransplantation is *"any procedure that involves the transplantation, implantation or infusion into a human recipient of either (a) live cells, tissues, or organs from a nonhuman animal source, or (b) human body fluids, cells, tissues or organs that have had ex vivo contact with live nonhuman animal cells, tissues or organs"* (FDA.gov). Organ transplant needs currently outpaces the supply with over ten patients die each day waiting for an organ transplant and xenotransplantation is one viable option.

IND PROCESS FOR BIOLOGICS – 21 CFR 312

The FDA regulates clinical studies in the US, and unapproved drugs and biologics must be conducted under an Investigational New Drug Application (IND). The IND is continually updated with new protocols, study data, and annual reports. The IND for a biologic must contain administrative information, preclinical research results, any previous human experience with the drug (i.e., outside the US), chemistry/ manufacturing/ control (CMC), and the clinical protocol. It's important to reiterate *the IND is never approved, rather, it is: pending, active, on hold, or a partial hold*. To learn more about IND in biologics, the OCTGT has a website called OCTGT Learn. On the site, there are many videos and activities to find out more about the approval process for Biologics including this video on IND approvals.

Let's Explore!

Biologics Products & Establishments Product Approvals & Clearances, Product/Manufacturer Lists, Other Resources are found at this web page. Approved Biologics are listed at the FDA website here: Approved Biologics. Take a look around the site – are there any classes of biologics that surprise you that the CBER regulates? https://www.fda.gov/BiologicsBloodVaccines/ucm121134.htm

a. Search For the 2016 biological approvals. How many BLAs were approved in 2016? How many Device biological approvals?
b. Find a BLA – either biological or biological device, 2015-present, that interests you. Summarize the product information and supporting documents.

SUBMITTING A BLA

Biologic license applications (BLAs) are the formal submissions of data when companies are seeking approval to market a biologic in the United States. BLAs for biologics are submitted to CBER, and BLAs for well-characterized proteins are submitted to CDER. BLAs are similar to an NDA in that they must provide the efficacy and safety information required for approval for use in humans; administrative information, CMC information, preclinical and clinical studies, and labeling. There are two different types of BLAs: full, *stand-alone BLAs (351(a))* filed for approval of an originator biological product, and *abbreviated BLAs (351(k))* filed for approval of a biosimilar product. The BLAs are regulated under 21 CFR Parts 600-680. BLAs must contain the administrative information, the CMC, preclinical studies, clinical data, and labeling.

THE PURPLE BOOK

"In 2014, the FDA released the Purple Book, a listing of all biological products. The Purple Book will serve as a helpful resource to assist the pharmaceutical industry determining the earliest date at which a biosimilar or interchangeable product could be licensed. Because biosimilar and interchangeable biological products will be listed under the corresponding reference product, users can also easily see if there is a biosimilar product or interchangeable biological product licensed" (FDA.gov). Explore the purple book, here: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm411418.htm

BIOSIMILARS & BPCI ACT

In 2010, President Obama signed into law the *Affordable Care Act*, which included the Biologics Price Competition and Innovation Act (*BPCI Act*) - an amendment of the *PHS Act* - to create *an abbreviated licensure pathway for products that are demonstrated to be 'biosimilar.*' Biosimilars are biotherapeutic products that are interchangeable (similar regarding efficacy, safety, and quality) with the FDA-licensed product. *They are not 'generic' in that they are not exact copies*; the complexity of biologics precludes the ability for them to be identical.

The FDA has a multi-step approach for drug approval for biosimilars:

- Structural analysis
- Functional assays (ex. Bioassays)
- Animal data (ex. Toxicology)
- Human Clinical Studies

Approval of a biosimilar application may not occur until 12 years after the date on which the reference product was first licensed. Patents of biological products are started to expire by 2012, and we quickly saw approvals for biosimilars.

"On March 6, 2015, Zarxio obtained the first approval of FDA.[9] Sandoz's Zarxio is biosimilar to Amgen's Neupogen (filgrastim), which was originally licensed in 1991. This is the first product to be passed under the Biologics Price Competition and Innovation Act of 2009 (BPCI Act), which was passed as part of the Affordable Healthcare Act. However, Zarxio was approved as a biosimilar, not as an interchangeable product, the FDA notes. Moreover, under the BPCI Act, only a biologic that has been approved as an "interchangeable" may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product. The FDA said its approval of Zarxio is based on a review of evidence that included structural and functional characterization, animal study data, human pharmacokinetic and pharmacodynamics data, clinical immunogenicity data and other clinical safety and effectiveness data that demonstrates Zarxio is biosimilar to Neupogen." (Wikipedia, Biosimilar, 2017).

US approved biosimilars

Date of Biosimilar FDA Approval	Biosimilar Product	Original Product
March 6, 2015[18]	Filgrastim-sndz/Zarxio	filgrastim/Neupogen
April 5, 2016[19]	infliximab-dyyb/Inflectra	infliximab/Remicade
August 30, 2016[20]	etanercept-szzs/Erelzi	etanercept/Enbrel
September 23, 2016[21]	adalimumab-atto/Amjevita	adalimumab/Humira

BIOSIMILAR PRODUCTS – TERMINOLOGY

To understand biosimilar products and their regulation it is necessary to be clear on the terms used to describe these types of products. The FDA recently released a consumer update web page on Biosimilars. The following are definitions and explanations from the FDAs training website on biosimilars.

- "A generic drug is bioequivalent to a brand name drug in dosage form, safety, and strength, route of administration, quality, performance characteristics, and intended use. Generic drugs are chemically identical to the brand-name drug. As a result, different manufacturers can produce what are essentially exact copies of the brand name product" (fda.gov).

- "Biological products are medical products which are larger and more complex molecules than drugs, and therefore are harder to characterize. Many of these products are produced in a living system, such as a microorganism or plant or animal cell. The nature of biological products creates unique challenges that do not exist in small molecule drugs. There are many types of biological products" (fda.gov).
- "A reference product is a biological product approved by the FDA under the Public Health Service Act based on a full complement of product-specific data, including nonclinical and clinical data. A biosimilar product is approved based on a showing that it is highly similar and has no clinically meaningful differences regarding safety, purity, and potency (safety and effectiveness) from the reference product" (fda.gov).

- "A biosimilar product is a biological product that is highly similar to the reference product notwithstanding minor differences in clinically inactive components and has no clinically meaningful differences regarding safety, purity, and potency (safety and effectiveness) from the reference product. Biosimilar products will have some differences from the reference product because of the complexity and inherent variability of biological products. However, these differences must not result in clinically meaningful differences regarding safety, purity, and potency (safety and effectiveness) as compared to the reference product" (fda.gov).

Here is a comprehensive FDA course on Biosimilars. Perform the activities in this course and answer the questions below: http://fdabiosimilars.e-paga.com/

1. In your own words define a biosimilar product
2. What year were biosimilars approved for marking in the US?
3. What is the BPCI Act and why is it important here?
4. True or False: Biosimilars are more expensive than biological products?
5. What is the difference between a generic drug and a biosimilar – why isn't a biosimilar drug just called a generic drug?
6. What is a reference product?
7. True/False: The goal of a biosimilar product development program is to demonstrate biosimilarity between the proposed biosimilar product and a reference product.
8. True/False: FDA intends to use a risk-based, totality-of-the-evidence approach to evaluating all available data and information submitted in support of biosimilarity of the proposed biosimilar product to the reference product.

COMPLEXITY OF BIOSIMILAR MANUFACTURING

There is an inherent variability like biological products – and it is important to ensure lot-to-lot variation is minimal and has no effect on safety and efficacy. A small change in production may have a significant effect on the product. Therefore, it's important to understand this variability to maintain product quality, potency, safety, and efficacy. The degree of variability should be characterized and controlled within specifications to assure lot-to-lot consistency. This variability is limited by testing the in-process material and final product to ensure that the important quality attributes of the product are kept within an expected range. According to the FDA, *Critical quality attributes are physical, chemical, biological, or microbiological properties or characteristics of a product that defines the products function, and may affect safety and efficacy.*

Here are some relevant specification terms to familiarize yourself with:

- *Acceptable Variability: Some degree of variability is acceptable as long as the intended use is unaffected by this variability.*
- *Variability Controls: Variability is tightly controlled by understanding, monitoring and validating the manufacturing process and assessed by lot release specifications.*
- *Specification Defined: "A specification is defined as a list of tests, references to analytical procedures, and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described" (fda.gov).*
- *Specification Criteria: Specifications establish the set of criteria to which a drug substance, drug product, or materials at other stages of the biological product's manufacturer should conform to be considered acceptable for its intended use.*
- *Lot Release Specification: Lot release specifications are quality standards that are proposed and justified by the manufacturer and approved by the FDA as conditions of approval to ensure the product is safe and effective over its shelf life.*

ABBREVIATED APPROVAL PATHWAY

A biosimilar product can be approved based on existing knowledge about reference product – including safety and effectiveness of the reference product. The goal of approval is to demonstrate it to be biosimilar to a reference product and allows products are manufactured faster and at a lower cost than other biologicals without having to repeat clinical studies in humans. The important aspect of the abbreviated approval pathway is a robust analytical characterization of the product, which must demonstrate through structural and functional testing the product to be biosimilar to the reference product. All the general requirements in place for a biological product apply to a biosimilar product including a comprehensive CMC in addition to following CGMP regulations. Although this abbreviated pathway offers a shorter timeline for approval of the biosimilar product, this product must still meet the same manufacturing

standards as a biological product. The FDA has a rigorous and science-based approach for development and approval of biosimilar products.

CHARACTERIZATION OF A BIOSIMILAR

1. Analytical Studies
2. Animal Studies
3. Clinical PK/PD studies
4. Clinical Immunogenicity assessment
5. Additional Clinical Studies

There is one important point to note about any differences that arise. This from FDA's training website on biosimilars: *Residual uncertainty about biosimilarity is a concept related to differences observed between the proposed biosimilar product and the reference product, and whether those differences could affect safety, purity or potency (safety and effectiveness). When differences are identified, they must be evaluated to determine potential impact. Any potential impact of the differences in safety, purity or potency (safety and effectiveness) should be addressed and supported by appropriate data and information.* If there is any uncertainty of biosimilarity of the product to the reference standard after completing analytical, animal and PK/PD studies, and immunogenicity assessment, the manufacturer may have to perform additional clinical data to address this uncertainty. The FDA uses the data in its entirety on a risk-based assessment to approve the product.

PREAPPROVAL INSPECTIONS FOR BIOLOGICS

Part of the BLA process includes a pre-license inspection as outlined in the CFR. The inspector is looking for all the related operation facilities during all phases of manufacturing. These checks typically happen about halfway through the review cycle. The Division of Manufacturing and Product Quality in CBER's Office of Compliance and Biologics Quality (OCBQ) are responsible for the inspections of biologic drugs and devices. The Division of Blood Applications in CBERS OBRR is the lead for blood and blood product applicant inspections.

OFFICE OF COMPLIANCE & BIOLOGICS QUALITY ACTIVITIES

The compliance activities related to biologics are customarily overseen by CBER's Office of Compliance & Biologics Quality (OCBQ). The OCBQ has many important activities within CBER and the approval of a biologic including inspection and compliance activities, pre- and post-market approval activities and compliance. It's important to note here that the FDA has limited recall authority – and recall of biologic products is voluntary. If CBER identifies areas of noncompliance it may issue a Regulatory Action Letter, revocate the BLA that has been published on that product (or even other products from the same company/facility), seizure, and injunction as well. More on FDA enforcement in a later chapter. Below is an overview of compliance activities of the OCBQ. This excerpt if from the OCBQ website: https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ucm331317.htm

OCBQ Inspection, Surveillance, and Compliance Activities (From fda.gov)

- "Ensures the quality of products regulated by CBER over their entire lifecycle through pre-market review and inspection, and post-market review, surveillance, inspection, outreach, and compliance.
- Monitors the quality of marketed biological products through surveillance, inspections, and compliance programs; reviews, evaluates and takes appropriate compliance action
- Reviews and evaluates all administrative action recommendations including suspension, revocation, denial of a license, disqualification of investigators, and recommended civil and criminal actions, including seizures, injunctions, and prosecution based on findings of inspections and investigations
- Directs the biologic product shortages program for CBER-regulated products.
- Directs the recall program for CBER-regulated products.
- Directs CBER's bioresearch monitoring program, and takes appropriate compliance actions
- Biological Product Deviation and Blood Collection and Transfusion Related Fatality Reports"

OCBQ Pre- and Post-Market Approval Activities (From fda.gov)

- "Leads pre-approval and pre-license inspections
- Provides assessment of the compliance status of regulated establishments within CBER's purview
- Evaluates proposed proprietary names to avoid potential medication errors related to look-alike and sound-alike proprietary names and mitigating other factors that contribute to medication errors
- Provides consultative reviews of proposed product labeling.
- Plans and conducts tests on biological products and conducts research to develop and improve procedures to evaluate the safety, efficacy, and purity of biological products.
- In cooperation with other Center components, as appropriate, tests biological products submitted for release by manufacturers."

Compliance-Related Policy Activities (From fda.gov)

- "Advises the Center Director and other Agency officials on emerging and significant compliance issues for biological products and serves as CBER's focal point for surveillance and enforcement policy."
- Develops, with other CBER/Agency components, policies and compliance standards for biological products, including Current Good Manufacturing Practice (CGMP) regulations; ensures the uniform interpretation of standards and evaluates industry's conformance with CGMP in manufacturing biological products.

Test yourself! Learn more in this self-paced learning module from the FDA. Perform the quiz at the bottom. https://www.accessdata.fda.gov/scripts/cderworld/index.cfm

a. Did you learn anything new?
b. Knowledge Check:

Which of the following does not fall within the definition of a biological product?

- Vegetable extract
- Virus
- Vaccine
- Toxin and antitoxin

What is understood by the term "comparability" as used by FDA?

- It defines the applicable parameters relating to drug scalability.
- It is a table of molecular equivalencies for determining the meta-identity of drugs.
- It refers to the comparison of a biological product before and after a manufacturing change.
- It establishes a sequence of cross-referential indices used in the approval process.

Which of the following is not a similarity between a new drug application and biologics license application?

- Both have a fast-track designation.
- Both require financial disclosure.
- Both have pediatric study requirements.
- Both obtain their regulatory power from the Public Health Service Act.

LABELING. Labeling here is referring to the display of written or printed material on the container or an enclosed document. Labeling includes both FDA approved labelings such as container labels, professional labeling in the package insert (PI – prescribing information), patient labeling (PPI – patient package insert), medication guides, and instructions for use. But also any promotional material.

There are four prescription drug labeling types:

1. Professional labeling
2. Patient labeling
3. Container and carton labels
4. Structure product labels (SPL)

Professional Labeling: Also referred to as prescribing information and package insert contains the necessary information for a safe and effective product for use by the healthcare provider (doctor). The Physician Labeling Rule (PLR) applies here and is covered by 21 CFR 201.56-57. This label has three sections: Full prescribing information, highlights of prescribing information, and the table of contents.

Patient Labeling: This includes PPI and medication guides for patients and is covered by 21 CFR 208.1(a) and (b). Medication guides are required when it could help prevent a severe adverse effect by providing the patient with information about a known serious side effect and how the patient should adhere to the directions of use when crucial to the effectiveness of the drug.

Container Label: The container or carton labels for biologicals are covered under 21 CFR 610.60-61 and must contain the name of the product, the manufacturer's name and contact information, lot identifiable number, expiration date, recommended dose, for prescriptions must state 'Rx only,' and must include the medication guide. In certain cases, this list may be expanded to include such things as storage conditions, preservatives, adjuvant if present and product source.

Structured Product Label (SPL): SPLs are posted publically at http://labels.fda.gov/ an online label repository, which allows consumers to research labels and download information from this repository. The purpose of this site is to provide a single place where healthcare providers can access accurate and up to date information quickly.

ADVERTISING & PROMOTION

The FDA distinguishes in its regulations between promotional and non-promotional activities. Product communications intended to be non-promotional must not make product claims, or they will be subject to FDA regulations. Regulated promotional materials may include advertisements on TV, in magazines, on the radio and even in social media! For prescription advertising, the FDA has jurisdiction, and both CDER and CBER are responsible for promotional labeling for biologics. In CBER, APLB oversees labeling (OPDP in CDER). The bottom line for advertising is the labeling must be consistent with the FDA-approved labeling, must be backed by considerable evidence and must not be misleading.

Summary

- ✓ A therapeutic biological product is any virus, serum, toxin, vaccine, blood component, or allergic product
- ✓ CBER has regulatory authority over biological products, except therapeutic proteins which are overseen by CDER
- ✓ BLAs are similar to NDAs and required to bring biological products to market
- ✓ The *BPCI Act* created an abbreviated pathway for biosimilars, products that have the therapeutic equivalence of an approved biologic reference product
- ✓ Complexities of biological products create manufacturing challenges

CHAPTER 8: MEDICAL DEVICE & COMBINATION PRODUCTS

OBJECTIVES:

- ✓ Understand how the FDA classifies a medical device – using the FDA website look up medical device products and their approval.
- ✓ Describe how FDA regulates approvals: PMN, PMA, IDE, and IRB.
- ✓ Understand regulations that govern medical devices and know how to look up these regulations on the FDA website.
- ✓ Explore and apply CFR 820.
- ✓ Understand how the FDA determines which regulatory pathway (center overseeing product), and why.
- ✓ Differentiate between Class I, II, & III medical devices.
- ✓ Distinguish between IVD, IUO, RUO, LTD, GPR, & ASR.
- ✓ Understand ISO 13485 and why it is important in device regulation even though it is regulated by the FDA through CFR 820.
- ✓ Provide examples of combination products how the FDA determines regulatory authority.

INTRODUCTION TO MEDICAL DEVICES

Defining what a medical device is can be a bit complex. A medical device can range from a Band-Aid to a tongue depressor, to a clinical testing kit, to a replacement hip. Due to the functional complexity of devices and combination applications (for example birth control implants), the regulations can also be very complex and specialized as well. In this chapter, we will look at a broad overview of medical device regulation including different categories of devices, regulations that apply, and the approval process.

The official definition of a medical device as defined by 201(h) of the *FD&C Act*: "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article 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 intended to affect the structure or any function of the body of man or other animals..." (fda.gov)

Let's Explore!

Explore at the FDA website examples of medical devices: What are some examples of items you didn't know are classified as devices?(look at the left-hand tabs)

The FDA began regulating medical devices in 1938 under the *FD&C Act*. Under this act, the FDA focused on adulteration but not safety. It was not until the 1960s where the FDA began looking at areas of safety and effectiveness and was amended in 1976 to include setting standards and premarket approval.

The Center for Devices and Radiological Health (CDRH) oversees the regulation of medical devices and radiation-emitting products, however, in 1991 *the FDA created an inter-center agreement that gave the Center for Biologics Evaluation and Research (CBER) full responsibility to devices related to blood and cellular products.* Later on combination products. Medical devices must be registered and listed with the FDA. Even

if they do not sell the device here in the US, they still must register with the FDA. The CDRH department has an entire website dedicated to medical device training called CDRHLearn. It can be found here.

CDRH ORGANIZATION

- Office of the Center Director
- Office of Communication and Education
- Office of Compliance
- Office of Device Evaluation
- Office of In Vitro Diagnostics and Radiological Health
- Office of Management Operations
- Office of Science and Engineering Laboratories
- Office of Surveillance and Biometrics

MEDICAL REGISTRATION (21 CFR 807): All medical devices (both domestic and foreign) must be registered and listed with the FDA.

Let's Explore!

Go to CDRHLearn https://www.fda.gov/Training/CDRHLearn/default.htm and Click on "Start here," click on "Overview of Regulatory Requirements" video, and watch this comprehensive 30min video on medical device regulation. Provide any interesting notes below.

CLASSIFICATION OF A MEDICAL DEVICE! (21 CFR 860):

Medical devices are regulated based on the relative risk posed by the product and organized by class. A Class I device is the lowest risk device, Class II is an intermediate risk and, Class III are high-risk devices.

Class I: A Class I device is a relatively low-risk device with minimal safety considerations for the consumer; safety is assured through a general set of guidelines called "general controls." Examples of a Class I device include prescription sunglasses or elastic bandages. There are currently approximately 780 Class I devices on the market. General Controls include Adulteration / Misbranding, Electronic Establishment, Registration, Electronic Device Listing, Premarket Notification [510(k)], Quality Systems, Labeling, and Medical Device Reporting (MDR).

Class II: Most devices are classified Class II, an intermediate-risk device that is subject to "special controls" to assure safety. The majority of Class II devices are subject to premarket review and clearance by FDA through the 510(k) pre-market notification process and may have rigorous review requirements in-line with a class III device. Examples include pregnancy tests and motorized wheelchairs. There are currently over 800 Class II devices on the market.

Class III: A Class III device is a high-risk device and includes devices that may be implanted or support life. Also, devices that are new in technology and there is no substantially equivalent device currently available must follow Class III regulations. Examples of a class III device include a pacemaker. Class III devices are subject to the most rigorous review process that includes general controls, special controls, and premarket approval. There are fewer than 120 Class III devices currently on the market.

Let's Explore!

LEARN MORE!
https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice/
Classify your medical device! ☺ Go into the Classification database and search for "wheelchair." What classification comes up? Search for a device you're curious about.

"Most medical devices can be classified by finding the matching description of the device in Title 21 of the CFR, Parts 862-892. FDA has classified and described over 1,700 distinct types of devices and organized them in the CFR into 16 medical specialty panels such as cardiovascular devices or in vitro diagnostics" (FDA.gov).

Medical Device Classification: 21 CFR 862-892

862 = Chemistry/Toxicology	878 = General Plastic Surgery
864 = Hematology/Pathology	880 = General Hospital
866 = Immunology/Microbiology	882 = Neurological
868 = Anesthesiology	884 = Obstetrical/Gynecological
870 = Cardiovascular	886 = Ophthalmic
872 = Dental	888 = Orthopedic
874 = Ear, Nose and Throat	890 = Physical Medicine
876 = Gastro/Urology	892 = Radiology Regulations

For each of the devices classified, the CFR provides a description, which includes intended use, class the device belongs (i.e., Class I, II, or III), and marketing requirements.

Premarket Notification (PMN) 510(k), 21 CFR 807 subpart e: In section 510(k) of the *FD&C Act* device manufacturers are required to notify FDA their intent to market a medical device as a Premarket Notification (PMN) or 510(k). The purpose of a 510(k) is for a manufacturer to demonstrate that the device is as safe and effective (substantially equivalent) to a device already on the market. If FDA rules the device is "substantially equivalent" the manufacturer can market the device. Some Class I, most Class II, and a few Class III require a 510(k).

Premarket Approval (PMA) 21 CFR 814: A Premarket Approval (PMA) application must be submitted if a manufacturer wants to market a new product that differs from products already on the market. PMA only applies to Class III devices! "A PMA is the most stringent of the submissions and must provide valid scientific evidence collected from human clinical trials showing the device is safe and effective for its intended use. If the device is life sustaining or presents a potential, unreasonable risk of illness or injury, it may have special approval processes (under Class III)" (FDA.gov).

Investigational Device Exemption (IDE) 21 CFR 812: An IDE applies to devices correctly and the application of use in human clinical studies. All clinical evaluations of investigational devices require an approved IDE. Depending on the class of device (Class I, II, or III) the application may take a different regulatory route. For example, a Class III device requires a Pre-Market Application (PMA) and clinical studies, a Class II may not require clinical studies, and Class I do not need FDA approval to market the product (but it must be registered with FDA). More on devices in a later chapter!

Let's Explore!

Good Clinical Practices in Medical Devices: 21 CFR 812: To learn more, watch the video on Medical Device IDE clinical study here: From IDEA to IDE:
http://fda.yorkcast.com/webcast/Play/46344ca5abbb465e88404a92eed542f71d

In addition, here: GCP in medical devices:
http://fda.yorkcast.com/webcast/Play/477af877491747379c36c4ab1c7421b9

Institutional Review Boards (IRB): Device clinical studies are monitored by the Institutional Review Boards (IRB) located at clinical studies site. Recall the IRB purpose is to ensure ethical practices such as informed consent and patient selection criteria. If the IRB determines that a device is a significant risk the patient, they must submit an IDE application to the FDA. The FDA must approve the application before the applicant enrolling patients in the clinical study.

If the IRB determines that the device is not a significant risk, they may enroll patients without submitting an IDE. The clinical study will be monitored by the IRB under the IDE regulations in 21 CFR 812.2(b). Confidentiality requirements ensure the FDA will not disclose the existence of an IDE.

This review process is not only rigorous, but it is also expensive. The FDA reported, in 2013 the PMA process fee was $248,000, and the 510(k) processing fee was an additional $4,900.

Decorative Contact Lenses – A Case Study: Watch this video on decorative contact lenses.

a. Why are decorative contact lenses considered devices?
b. What are the risks of decorative contact lenses?
c. Imagine you are a company wanting to sell a decorative contact lens. Map out your application process, consider:
    a. What class of device?
    b. What Center will you contact?
    c. Will you require PMN, PMA, IDE, or IRB?

IN VITRO DIAGNOSTICS (IVDS)

In vitro diagnostics (IVDs) are tests that can detect diseases, conditions, or infections. Some tests are used in the laboratory, or other health professional settings and other tests are for consumers to use at home. The Office of *In Vitro* Diagnostics and Radiological Health (OIR) oversees regulations about IVDs. The FDA has defined more than 500 different IVDs in the US, and worldwide earn more than $50 billion dollars annually.

Research Use Only (RUO) & Investigational Use Only (IUO): Both of these IVDs are considered to be pre-commercial since they are not used for diagnostic purposes and do not have to follow the strict labeling requirements that apply to commercial diagnostic IVDs. The labeling needs of these are found in 21 CFR 809.10. The difference between RUO and IUO is that RUO is for research only, but IUO may be pre-shipped and may be evaluated for future use as an IVD.

General Purpose Reagents (GPR) & Analyte Specific Reagents (ASR): GPR has a general laboratory application, and is a Class I device. As such, Class I devices are exempt from PMN. ASR is a little more complicated in that they can be used as a Class I, II or III device depending on its application. ASR devices can range from antibodies to nucleic acid binding proteins used for diagnostics in blood banking samples (class II) to a test for Ebola (Class III).

IVD Classification: IVDs can be classified I, II or III depending on their application; diagnosis, monitoring, patient population, type of specimen and the consequence of a false test result. For example, if a false test results in the amputation of a leg due to suspected cancer, this would be classified a Class III IVD. Approximately 8% of IVDs on the market are Class III. This classification determines the regulatory pathway for the device.

Under the inter-center agreement, both CDRH and CBER oversee IVDs. The Office of Blood Research and Review (OBRR) within CBER manages the pre-market review and post-market surveillance for IVDs assigned to CBER, whereas the Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD) within CDRH administers the pre-market review and post-market surveillance for IVDs assigned to CDRH. OIVD is also responsible for CLIA waivers (see below). Manufacturers apply for the CLIA determination during the pre-market review process.

LABORATORY DEVELOPED TESTS (LDT)

The following excerpt is from the FDA website: https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/LaboratoryDevelopedTests/default.htm

"A laboratory-developed test (LDT) is a type of in vitro diagnostic test designed, manufactured and used within a single laboratory. LDTs can be used to measure or detect a wide variety of analytes (substances such as proteins, chemical compounds like glucose or cholesterol, or DNA), in a sample taken from a human body" (FDA.gov).

LDT's are important to the continued development of personalized (point-of-care) medicine (such at a hospital or doctor's office). It is also essential that in vitro diagnostics are accurate so that patients do not seek unnecessary or inappropriate procedures or delay treatments. The FDA has not enforced premarket review and other applicable FDA requirements because LDTs were relatively simple lab tests and available on a limited basis. However, due to advances in technology and business models, LDTs have evolved and proliferated significantly since the FDA first obtained authority to regulate all in vitro diagnostics as devices in 1976.

"The FDA has identified problems with several high-risk LDTs including claims that are not adequately supported by evidence; lack of appropriate controls yielding erroneous results, and falsification of data. The FDA is concerned that people could initiate unnecessary treatment or delay or forego treatment altogether for a health condition, which could result in illness or death. The FDA is aware of faulty LDTs that could have led to patients being overtreated or undertreated for heart disease; cancer patients being exposed to inappropriate therapies or not getting effective treatments; incorrect diagnosis of autism; unnecessary antibiotic treatments; and exposure to unnecessary, harmful treatments for certain diseases such as Lyme disease" (FDA.gov).

To assist healthcare providers in guiding treatment and encouraging the advancement of personalized medicine, the FDA notified Congress of their intent to issue a draft oversight framework for LDTs based on risk to patients. This draft oversight framework includes a pre-market review for higher-risk LDTs, like those used to guide treatment decisions, including the many companion diagnostics that have entered the market as LDTs. In addition, under the draft framework, the FDA would continue to exercise enforcement discretion for low-risk LDTs and LDTs for rare diseases, among others. The framework would be phased in over many years. The purpose of the guidance is to spur partnerships that may result in encouraging new therapies for patients living with serious and life-threatening diseases.

COMPANION DIAGNOSTICS

The following excerpt is from the FDA website:
https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm407297.htm
"A companion diagnostic is a medical device, often an in vitro device, which provides information that is essential for the safe and effective use of a corresponding drug or biological product. The test helps a health care professional determine whether a particular therapeutic product's benefits to patients will outweigh any potential serious side effects or risks. If the diagnostic test is inaccurate, then the treatment decision based on that test may not be optimal" (FDA.gov).

Companion diagnostics can:

- ✓ identify patients who are most likely to benefit from a particular therapeutic product;
- ✓ identify patients likely to be at increased risk for serious side effects as a result of treatment with a particular therapeutic product, or
- ✓ monitor response to treatment with a particular therapeutic product for the purpose of adjusting treatment to achieve improved safety or effectiveness" (FDA.gov)

CLINICAL LABORATORY IMPROVEMENT AMENDMENTS (CLIA)

The following excerpt is from the CLIA website: https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/Program_Descriptions_Projects.html

"In 1988 the Clinical Laboratory Improvement Amendments (CLIA) was established to define quality standards for all laboratory testing to ensure accuracy, reliability, and timeliness of patient test results regardless of where the test was performed. Final regulations were established in 1992.
Three federal agencies are responsible for CLIA: The Food and Drug Administration (FDA), Center for Medicaid Services (CMS) and the Center for Disease Control (CDC). Each agency has a unique role in assuring quality laboratory testing" (CMS.gov).

FDA

- ➢ Categorizes tests based on complexity
- ➢ Reviews requests for Waiver by Application
- ➢ Develops rules/guidance for CLIA complexity categorization

CMS

- ➢ Issues laboratory certificates
- ➢ Collects user fees
- ➢ Conducts inspections and enforces regulatory compliance
- ➢ Approves private accreditation organizations for performing inspections, and approves state exemptions

- Monitors laboratory performance on Proficiency Testing (PT) and approves PT programs
- Publishes CLIA rules and regulations

CDC

- Provides analysis, research, and technical assistance
- Develops technical standards and laboratory practice guidelines, including standards and guidelines for cytology
- Conducts laboratory quality improvement studies
- Monitors proficiency testing practices
- Develops and distributes professional information and educational resources
- Manages the Clinical Laboratory Improvement Advisory Committee (CLIAC)

MEDICAL DEVICE LABELING

Any label or written material on the device or material that accompanies the device. Labeling must provide adequate directions for use unless exempt and labeling must not be false or misleading. Labeling must have adequate directions for use, proper operating instructions, and warnings where the device's use may be dangerous. The FDA recognizes three types of labeling for devices. A. FDA-approved labeling. B. FDA-promotional labeling and C. Package-insert labeling. The basic outline for labeling specific to medical devices includes The manufacturer, Device name, Description, Indication, Contraindications, Warnings, and Precautions, Use in Specific Populations, Prescription device statement, Adverse reactions, and Date of issue. To learn more about device labeling see Guidance's here: https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/DeviceLabeling/default.htm

Labeling Enforcement

FDA can enforce labeling violations through Notices of Violation (NOVs), Warning Letters, or judicial action (consent decrees, injunctions, and seizures). The FDA looks at a company's website, videos, commercials, brochures, bulk mailings and press releases to determine if there is any misrepresentation of labeling a device. The FDA responds to violations with the least stringent action depending on the potential to jeopardize public health.

MISBRANDING

Section 502 of the FFDCA contains provisions on misbranding and false or misleading labeling. A device is considered misbranded if it is false or misleading in any way and if it does not include adequate directions for use. Other examples of misbranding from the FDA website:

- "It is in package form, and its label fails to contain the name and place of business of the manufacturer, packer, or distributor; and an accurate statement of the contents regarding weight, measure, or numerical count;
- Any required wording is not prominently displayed as compared with other wording on the device, or is not clearly stated;
- It is dangerous to health when used in the dosage or manner or with the frequency or duration prescribed, recommended or suggested in the labeling;
- If the device's established name (if it has one) its name in an official compendium or any common or usual name is not prominently printed in type at least half as large as that used for any proprietary name;
- If the establishment is not registered with FDA as per Section 510, has not device listed as per section 510(j), or obtained applicable premarket notification clearance as per Section 510(k);
- If the device is subject to a performance standard and it does not bear the labeling prescribed in that standard" (FDA.gov).

QUALITY SYSTEM (QS) REGULATION – CFR 820

"CFR 820 covers the design and manufacture of devices sold in the US and is similar to ISO 13485. Part of this regulation states manufacturing facilities will be inspected by the FDA. The quality system regulation includes requirements related to the methods used in and the facilities and controls used for designing, purchasing, manufacturing, packaging, labeling, storing, installing and servicing of medical devices. Manufacturing facilities undergo FDA inspections to assure compliance with the QS requirements. Quality System Guidance's are found here" (FDA.gov).
https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/QualitySystemsRegulations/default.htm

Code of Federal Regulations (CFR) Citations

- 21 CFR Parts 50, 56, 812: Clinical Studies
- 21 CFR Part 807
  - Establishment Registration and Listing
  - Premarket Notification [510(k)]
- 21 CFR Part 814: Premarket Approval (PMA)
- 21 CFR Part 812: Investigational Device Exemptions
- 21 CFR Parts 801, 809, 812, 820
  - Medical Device Labeling
- 21 CFR Part 820: Quality System Regulation
- 21 CFR Part 821: Tracking Requirements
- 21 CFR Part 803: Medical Device Reporting

The flexibility of the QS Regulation: "The QS regulation for devices embraces the same "umbrella" approach to the CGMP regulation of drugs. Because the regulation must apply to so many different types of devices, the regulation does not prescribe in detail how a manufacturer must produce a specific device. Rather, the regulation provides the framework that all manufacturers must follow by requiring that manufacturers develop and follow procedures and fill in the details that are appropriate to a given device according to the current state-of-the-art manufacturing for that specific device.

Manufacturers should use good judgment when developing their quality system and apply those sections of the QS regulation that apply to their specific products and operations, 21 CFR 820.5 of the QS regulation. Operating within this flexibility, it is the responsibility of each manufacturer to establish requirements for each type or family of devices that will result in devices that are safe and effective. The responsibility for meeting these needs and for having objective evidence of meeting these requirements may not be delegated.

Because the QS regulation covers a broad spectrum of devices, production processes, etc., it allows some leeway in the details of quality system elements. It is left to manufacturers to determine the necessity for, or extent of, some quality features and to develop and implement specific procedures tailored to their particular processes and devices" (FDA.gov).

INTERNATIONAL HARMONIZATION

The FDA has been a strong advocate for international harmonization of regulations. They worked in collaboration with the Global Harmonization Taskforce (GHTF) to develop QSR that promotes incorporation of international harmonization. In 2011, the GHTF re-organized to become the International Medical Device Regulators Forum (IMDRF) which include representatives from the US, Canada, Australia, Brazil, Japan and Europe. More information can be found here: http://www.imdrf.org/

ISO DEVICE REGULATIONS – ISO 13485

ISO 13485 is the standard for a quality management system for the design and manufacture of medical devices. Although ISO 13485 is a stand-alone document, is harmonized with ISO 9001 with a few important exceptions: It does not need to demonstrate continual improvement, and it does not have customer satisfaction requirements. What it does have, is a *focus on risk management and design control, which is essential for device manufacturing*. ISO 3485 also includes inspection and traceability requirements for implantable devices. It promotes awareness of regulatory requirements but also in-line with IMDRF.

POST-MARKET ACTIVITIES

The FDA requires medical device manufacturers to participate in many post-market activities; maintaining a quality system, inspections, post-market surveillance studies, tracking, reporting device malfunctions and injury and death.

Medical Device Reporting (MDR) 21 CFR 803: If a device causes a death or serious injury, it must be reported. There are also instances where malfunctions must also be reported and allows the FDA to monitor problems. The report must be made within 30 days, and there is a form and a website called Med Watch.

Medical Device Recall: A medical device recall is an action that takes place to address a problem with a medical device that may be in violation of an FDA law. Recalls occur when the device is defective, it causes a risk to health, or both. A recall does not necessarily mean the product must be returned, sometimes it just needs to be adjusted, or clarification safety instructions provided. 21 CFR 7 provides guidance so that responsible firms may conduct an active voluntary recall.

Examples of the types of actions that may be considered recalls:

- ✓ Inspecting the device for problems
- ✓ Repairing the device
- ✓ Adjusting settings on the device
- ✓ Re-labeling the device
- ✓ Destroying device
- ✓ Notifying patients of a problem
- ✓ Monitoring patients for health issues

A recall is either a correction or a removal of a product. A Correction addresses a problem with a medical device where it is used or sold; a Removal addresses a problem with a medical device by removing it from where it is used or sold. *In most cases, a company voluntarily recalls a device on its own.* When the company has violated an FDA law, the company must recall the device (correction or removal) and notify the FDA. *Legally, the FDA can require a company to recall a device if a company refuses to do so under 21 CFR 810, Medical Device Recall Authority.* 21 CFR 810 describes the procedures the FDA follows in exercising its medical device recall authority under section 518(e) of the FD&C Act.

It is important to note that a recall does not include a market withdrawal or a stock recovery. When there is a minor infraction not subject to legal action, the FDA may approve a market withdrawal. In the end, almost all recalls are conducted on a voluntary basis by the manufacturer.

A list of recalls by date, https://www.fda.gov/Safety/Recalls/ and a comprehensive searchable recall device database is here. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRES/res.cfm Device recalls following the same general recall procedure as previously discussed for drugs, which includes classification of recall (I, II or III), developing a recall strategy, and providing the FDA with recall status reports. To learn more about Device Recalls, visit the FDA device recall web page, and watch the FDA Video here. http://fda.yorkcast.com/webcast/Play/1b95461f64be40ecbe3415195cb39491d

COMBINATION PRODUCTS

"One of the more challenging regulated products is combination products. Combination products are therapeutic and diagnostic products that combine drugs, devices, and biological products. Although each have clearly defined regulatory guidance's in place, a combination of one or more of these creates a new product with a unique regulatory pathway. An asthma inhaler is an example of a combination device; it includes both the asthma drug and the device to get the drug to the lungs. Other examples of combination products found on the FDA website. Technological advances continue to merge product types and blur the historical lines of separation between FDA's medical product centers, which are made up of the Center for Biologics Evaluation and Research (CBER), the Center for Drug Evaluation and Research (CDER), and the Center for Devices and Radiological Health (CDRH)" (FDA.gov).
https://www.fda.gov/CombinationProducts/AboutCombinationProducts/ucm101598.htm

"Combination products raise challenging issues in both the FDA as well as the manufacturer. Differences in regulatory pathways for each component can impact the regulatory processes for all aspects of product development and management, including preclinical testing, clinical investigation, marketing applications, manufacturing and quality control, adverse event reporting, promotion and advertising, and post-approval modifications" (FDA.gov).

REGULATORY HISTORY: Combination product regulations were first provided in 1990 by the Safe Medical Device Act (SMDA). A provision was added (Section 503(g)) of the FD&C Act, requiring "combination products be assigned to a lead agency based on its Primary Mode of Action (PMOA)." In Title 21 of the Code of Federal Regulation (CFR) part, 3 established a Request for Designation (RFD) process which allows the FDA to provide guidance on which Center to be assigned to a product without a clear (or disputed) pathway. In 2002, the FDA (thru the Medical Device User Fee and Modernization Act (MDUFMA)), amended Section 503(g) mandated the FDA to establish an Office of Combination Products (OCP). The OCP was set up to work with FDA centers to develop guidelines and regulation to clarify combination product regulatory pathway.

OFFICE OF COMBINATION PRODUCTS: The OCP is responsible for combination product assignment, coordinating premarket review with the Centers involved, and ensure consistent post-market regulation. In addition, they examine and revise Guidances and practices unique to combination products. The bottom line – they serve as a facilitator of clearing combination product issues – but do not review the products themselves.

WHAT IS A COMBINATION PRODUCT? – 21 CFR 3.2(e): A combination product is defined in 21 CFR 3.2(e) as two or more regulated products; chemically or physically combined (21 CFR 3.2(e) (1)), or co-packaged (21 CFR 3.2(e)(2)), or cross-labeled but separately packaged (21 CFR 3.2(e)(3)).

Let's Explore!

Explore at the FDA website for combination products examples of each of these products: https://www.fda.gov/CombinationProducts/AboutCombinationProducts/ucm101598.htm

a. Physically or chemically combined:
b. Co-packaged:
c. Cross-labeled:

DETERMINING REGULATORY PATHWAY

Primary Mode of Action (PMOA). *Regulations are based on the primary mode of action (PMOA) of that combination product (drug, device or biologic) which in turn dictates which center primarily oversees this approval (CDER, CBER or CDRH) in combination with all interested centers by committee.* If there is not a clearly defined determination, the device manufacturer may file a Request for Designation (RFD) with the FDA. An RFD compels the FDA to classify the product and indicate the primary review group. The FDA has established an algorithm for assigning combination products when a PMOA is not set up with "reasonable certainty."

The FDA defines PMOA as "the single mode (or greatest contribution) of action of a combination product that provides the most important therapeutic action of the combination product" (FDA.gov). For example, if a device is used to deliver a therapeutic drug, the PMOA would be the drug and the Center assigned would be CDER. When a single, clear, mode of action is not established, the FDA utilizes an 'assignment algorithm' to assign the Center to oversee the combination product. The FDA will consider the historical duties as well as the Center that may have the most expertise with similar products.

Request for Designation: It is highly recommended the manufacturer (sponsor) of the combination product seek assignment early in the process as this has a dramatic effect on regulatory strategy. When the PMOA is "clear" the sponsor may contact the OCP informally (phone or email) to seek advice – this process is not binding and is subject to change. The formal designation is made through a Request for Designation (RFD) – which is a written application for designation submitted to the OCP. In this formal written request, the sponsor must clearly state the product description, ingredients, and components. If any of this change, the designation is no longer binding (and you may need to reapply for an RFD. In the RFD you must also provide all known mode of action (MOAs), the sponsor's identification of the PMOA, and a description of any related products with their regulatory status. The sponsor is also required to provide a recommendation of assignment with reasons why you recommend that assignment.

Premarket Review: Although the assigned Center is responsible for the review, other centers may also be involved in the review depending on the product. The FDA has created a streamlined Standard Operating Procedures (SOP) for the Intercenter Consultative and Collaborative Review Process to assist FDA staff in handling combination product submissions. The lead center typically applies its regulatory pathway – however, some situations require multiple applications – especially those combination products where the goods are separate products themselves.

Summary

- ✓ The CDRH oversees regulation of medical devices
- ✓ Medical devices are a broad range of instruments that range from tongue depressors to wheelchairs, glucose test kits, and hip replacements
- ✓ There are three classes of medical devices; Class I is low risk, Class II is intermediate risk, and Class III is a high-risk device
- ✓ PMAs are required to market new medical devices, PMN are necessary a substantially equivalent device to one already marketed
- ✓ IDE applies to the use of devices in clinical studies
- ✓ IVDs are tests that can detect diseases, conditions or infections and can be classified as Class I, II or III depending on their application
- ✓ LDT is a type of in vitro diagnostic test for use in a lab
- ✓ CLIA was established to define quality standards for all laboratory testing to ensure accurate and reliable patient results
- ✓ ISO 13485 is the international standard for quality management system in medical device manufacturing
- ✓ The FDA has recall authority of devices
- ✓ The FDA uses the PMOA to determine the regulatory pathway of medical devices that are combination devices (a drug/biologic/device)

CHAPTER 9: REGULATION OF FOOD & OTHER PRODUCTS

OBJECTIVES

- ✓ Understand the FDA's regulatory authority over food
- ✓ Describe the regulatory functions of CFSAN, CVM, and CVB
- ✓ Understand how the FDA, EPA, and USDA together regulate GMOs and their main focus
- ✓ Explore the FSMA, and the five main elemental changes brought about in food safety including recall authority in food
- ✓ Understand what Medical foods are and how they are regulated
- ✓ Identify several veterinary products and how and why the FDA regulates them
- ✓ Explore how the FDA regulates cosmetics and why they regulate them

THE REGULATION OF FOOD

FDA authority over food comes from the *FD&C Act*, which defines food as *"articles used for food or drink for man or another animal, chewing gum and articles used for components of any such article."* (Federal Food, Drug, and Cosmetic Act, 1938). The FDA is responsible for the safety of all food including individual components of food, animal and pet food, and food ingredients. Their mission is to prevent food adulteration and ensure foods are safe, wholesome and sanitary in addition to providing accurately labeled food. (FDA, FDA.gov, 2016)

CENTER FOR FOOD SAFETY AND APPLIED NUTRITION

The regulatory Center for food in the FDA is *the Center for Food Safety and Applied Nutrition* (CFSAN) which oversees food safety and purity. It has the power to regulate all domestic and imported food except for meat, poultry, and eggs (those are regulated by USDA). They oversee the safety of food ingredients developed through biotechnology, dietary supplements, food additives, and proper labeling of food. CFSAN is also concerned with food contamination, such as biological pathogens and naturally occurring toxins. They are also responsible for the regulation and safety of cosmetics ingredients and finished products.

COLLABORATION WITH OTHER REGULATORY BODIES

"FDA regulates food and cosmetic products sold in interstate commerce. However, products made and sold entirely within a state are governed by that state. This means, the FDA maintains close communications and interagency agreements with other regulatory bodies including the U.S. Department of Commerce's National Marine Fisheries Service, the Centers for Disease Control and Prevention (CDC), the U.S. Department of Treasury's U.S. Customs and Border Protection, the Federal Trade Commission (FTC), the U.S. Department of Transportation (DoT), the Consumer Product Safety Commission (CPSC), and the U.S. Department of Justice (DoJ)" (FDA.gov).

COLLABORATION WITH ACADEMIA AND INDUSTRY

CFSAN is actively involved in several academic projects through its *Centers of Excellence (COE)* program. CFSAN has four COEs:

1. the National Center for Food Safety and Technology (NCFST) with the Illinois Institute of Technology
2. the Joint Institute for Food Safety and Applied Nutrition (JIFSAN) at the University of Maryland
3. the FDA COE for Botanical Dietary Supplement Research at the National Center for Natural Products Research (NCNPR), University of Mississippi
4. the Western Center for Food Safety (WCFS) with the University of California at UC, Davis

USDA. The FDA is not responsible for meat, poultry, and frozen and dried eggs, that purview belongs to the United States Department of Agriculture (USDA) (www.usda.gov). The USDA also contributes to nutrition research and public health education. A division of the USDA, the Animal and Plant Health Inspection Service (APHIS), regulates genetically engineered food plants.

EPA. The Environmental Protection Agency (EPA) (www.epa.gov) regulates pesticides and their use on food crops. It sets tolerance limits for pesticide residues in foods (which the FDA enforces), publishes "safe use" directives and establishes quality standards for drinking water. The EPA also has some regulatory authority over the release of genetically modified organisms into the environment.

MAINTAINING A SAFE FOOD SUPPLY

Although the U.S. food supply is among the world's safest, we do not have to go too far back in the news to realize our supply is not fallible. (FDA Food Recall, 2016). See the many FDA publications on Listeria outbreaks in food just in the last year! Read more here on the Listeria outbreak in Texas favorite Blue Bell ice-cream.

The food industry and manufacturing practices are widely varied, and therefore the possible potential areas of contamination are many, including pre-harvest, processing, packaging, and storage!

Some of CFSAN's current areas of food safety concern are:

- ✓ pathogens such as bacteria and viruses
- ✓ naturally occurring toxins such as mycotoxins
- ✓ dietary supplements
- ✓ pesticide residues
- ✓ toxic metals including lead
- ✓ particulate matter
- ✓ food allergens including wheat, nuts, and dairy
- ✓ added nutrient concerns
- ✓ dietary components and labeling
- ✓ Transmissible Spongiform Encephalopathy-type diseases
- ✓ product tampering

FOOD SAFETY

There are three major issues related to food safety that are the most common causes of regulatory enforcement actions, and which are the most closely monitored:

- ➢ Contamination by pathogens (e.g., E. coli, Listeria monocytogenes).
- ➢ Adverse effects of additives such as food coloring and sweeteners.
- ➢ Unintentional additives (e.g. pesticide residues).

The FDA has the authority to inspect any facility where food is manufactured, packaged or handled in any way. Contamination by pathogens is one of the most significant problems faced in the United States according to the Centers for Disease Control (CDC). It is estimated that food-borne illnesses affect 1 out of every 6 Americans at some point in their lives. Forty-Eight million people become sick due to foodborne pathogens each year, of which approximately 128,000 are hospitalized, and 3,000 died (FDA.gov). The USDA and FDA have active consumer education programs targeted towards preventing such illnesses by teaching consumers about safe handling and preparation of foods, the shelf life of various kinds of food and other common sense tips.

TEST YOUR KNOWLEDGE!

The CDC has posted a podcast discussing their 2010 report on estimates of illnesses due to eating contaminated food in the United States. Click here to listen:
https://www2c.cdc.gov/podcasts/player.asp?f=4485979
The CDC also publishes its Foodborne statistics here:
https://www.cdc.gov/foodborneburden/index.html
What germ is responsible for most food-borne illness? Deaths? Why?

Hazard Analysis Critical Control Points (HACCP). The quality program implemented for the meat and poultry industry is called Hazard Analysis Critical Control Points (HACCP). *The goal of the HACCP is the reduction of contamination throughout the key points of each part of the process responsible for bringing meats and poultry to the market: Production, Slaughter, Processing, and Distribution.* All of these represent parts of the process where harmful pathogens are introduced without quality controls in place. The implementation of HACCP complements the inspection process, not replace it. Instead, it represents an effort to build quality into the products from the start.

LEGISLATIVE ACTS THAT REGULATE FOOD & AGRICULTURE

The Food, Drug, and Cosmetics Act sets out broad regulations of both the food and drug industries. There are additional, specific acts that regulate the food and agricultural industry beyond the *FD&C Act*, which includes:

- *The Federal Insecticide, Fungicide, Rodenticide Act (FIFRA) of 1910.* The EPA is under this Act for regulating the distribution, sale, use, and testing of pesticides, including those that are the result of genetic modifications to organisms.
- The Federal Import Milk Act (1927)
- The Public Health Service Act (1944)
- *Federal Meat Inspection Act and the Poultry Products Inspection Act of 1957*. This Act authorizes USDA to inspect meat and poultry products for safety and accurate labeling.
- *The Federal Plant Act (FPPA)* FPPA regulates the introduction or release to the environment of "plant pests." Genetically engineered organisms are considered plant pests under this act.
- The Fair Packaging and Labeling Act (1966)
- *Toxic Substances Control Act (TSCA) of 1976.* Chemicals that may pose a threat to human health or the environment are regulated by the EPA, via the TSCA.
- The Infant Formula Act of 1980, as amended
- The Nutrition Labeling and Education Act of 1990
- The Dietary Supplement Health and Education Act of 1994
- Food Allergen Labeling and Consumer Protection Act of 2004
- Food and Drug Administration Amendments Act of 2007
- *Food Safety Modernization Act (FSMA) of 2011.*

FOOD SAFETY MODERNIZATION ACT (FSMA)

Food Safety Modernization Act (FSMA) FSMA, which was signed into law by President Obama on January 4, 2011, enables FDA to better protect public health by *strengthening food safety* measures. Under the new law, FDA now has much more effective enforcement tools to protect the food supply including the *authority to issue a mandatory recall order.* To learn more about FSMA regulatory implications see the FSMA Q&A factsheet.

In short, here are the main elements of FSMA:

1. Preventive controls - Provides FDA legislative mandate to require comprehensive, prevention-based controls across the food supply to minimize the likelihood of contamination occurring.
2. Inspection and Compliance – Allows FDA to enforce compliance through inspection.
3. Imported Food Safety - Importers must verify that their suppliers have adequate preventive controls in place to ensure the safety of food products being imported.
4. Response - FDA is given mandatory recall authority for all food products as well as expanded administrative detention of products that are potentially in violation of the law, and suspension of a food facility's registration.
5. Enhanced Partnerships - The legislation encourages strengthening existing collaboration among all food safety agencies.

FOOD INGREDIENTS

Although the FDA has little regulatory control over food before it goes to market, what it does have control over is food ingredients such as food additives. Food additives include intentional components added to food as well as unintentional additives from the manufacturing process. All food additives are approved before use – a list of approved food additives can be found on the FDA website. Any substance that the FDA considers *'Generally Recognized as Safe (GRAS)'* do not need be approved before use.
https://www.fda.gov/Food/IngredientsPackagingLabeling/FoodAdditivesIngredients/ucm091048.htm

REGULATION OF AGRICULTURAL BIOTECHNOLOGY & GMOs

What are Genetically Modified Organisms (GMOs)? *Genetically modified organism (GMO) refers specifically using genetic engineering to produce heritable improvements in an organism, such as with plants, animals or bacteria, for a specific use. Genetic engineering is the application of recombinant DNA (rDNA) technologies to living organisms to create new products or improve existing ones*. Agricultural Biotechnology encompasses a diverse set of tools used to alter living organisms for the purpose of creating or modifying agricultural products (this includes traditional breeding as well as genetic engineering).

The planting of genetically engineered crops was allowed for the first time in the United States in 1995. Today, it is estimated that over 90% of soy and over 80% of cotton and canola products come from genetically modified crops. Genetically modified crops were created to improve production and cut costs by improving insect resistance, virus resistance, herbicide tolerance and similar issues that affect commercial crops.

The use of GM crops is controversial, and there are many concerns about the technology that remain to be addressed. There are concerns about the health effects of GM crops as well as their impact on native plant species. Supporters of GM crop technology assert that these crops are safe, that they require fewer pesticides than traditional crops and could be the answer to ending starvation and disease in developing countries. Genetically engineered "golden rice," for example, contains three transplanted genes that cause the rice to produce beta-carotene, which is converted to vitamin A, a vital nutrient in the human diet. Vitamin A deficiencies are the world's leading cause of blindness. Engineering nutrition into crops may help combat these types of epidemics.

Labeling of GM crops is a hot button issue! See CFSAN's website for more information on food safety. Here is also a handy map of states in the U.S. that have enacted, or have pending legislation on both sides of the debate – requiring GM crops be labeled, or prohibiting GM crops from being labeled.
http://www.centerforfoodsafety.org/issues/976/ge-food-labeling/state-labeling-initiatives#

REGULATORY AGENCIES FOR GM CROPS

Three federal agencies evaluate new crop varieties developed using genetic engineering: the FDA, the USDA, and the EPA.

- ✓ FDA: Evaluates food and feed safety. The FDA's Center for Food Safety and Nutrition (CFSAN) and the Center for Veterinary Medicine (CVM) evaluate new GM crops. They look for increased allergens, toxins and changes in nutrition or composition. The FDA's main concerns here are threats to human health through food and threats to animal health through feed. What the FDA is comparing these genetically modified products to is their unmodified counterpart. The FDA may then issue a statement about the modified food's substantial equivalence but does not approve the food as "safe," per se.

- ✓ USDA: Ensures agricultural and environmental safety. The USDA through the Biotechnology Regulatory Service (BRS) office of the Animal and Plant Health Inspection Service (APHIS) regulates all GM crops before commercial release. The USDA's primary concern is whether the new plant will harm agriculture or the environment. The USDA's authority over these matters is derived from the Plant Protection Act of 2000.

- ✓ EPA: Evaluates food safety and environmental issues associated with new pesticides. The EPA regulates GM crops that have altered pesticide characteristics. Bt GM corn is an example of a product that the EPA would evaluate. Bt corn is genetically modified to contain what's known as a "Plant Incorporated Protectant" (PIP). In other words, the Bt corn produces its own insecticide. The EPA evaluates this type of product for its impact on the environment and human health.

Let's Explore!

Visit the EPA website: http://www.epa.gov/ Summarize the EPA mission statement in your own words.

1. EPA is currently responsible for regulating GMOs. Why do you think the EPA is concerned about GMOs?
2. What is the Food Quality Protection Act?

ASSESSING GM CROPS FOR SAFETY

No other agricultural products have been subjected to as much testing or regulation of GM crops. Traditional food safety principles apply to GM crops, and they are judged on allergenicity, toxicity, and nutrition. They are not judged by their method of production. Comparing GM crops to existing "established as safe" crops allows a determination to be that a GM crop is "as safe as" its traditional counterpart.

Case Study: You are part of an R&D team for a cereal manufacturer, Breakfast 'R Us. Your team is debating the use of genetically modified crops in their new breakfast cereal 'Sunshine Morning Crunch.' Using at least three different sources (site your sources), argue for OR against (pick one) the use of genetically engineered ingredients in your cereal. Remember, you are the R&D researcher, not the customer!

MEDICAL FOOD

Food can be more than meeting basic nutritional and safety standards – it can be used to reduce the risk of disease. These *medical foods* are distinguished from other foods in their formulation – specifically to treat a disease or disorder. They are intended for the specific management of a disease or disorder for which distinctive nutritional requirements exist based on scientific evidence. They are not the same as nutritional supplements. Medical foods are a distinct class of food because they are not classified as a food nor medicine. However, *this is food that the FDA intends to be used under medical supervision by a patient requiring medical care*.

Foods such as these, for *"special dietary uses*," were first brought up in regulation in 1941, and added to the *FD&C Act* in 1976. In 1988 Congress amended the *Orphan Drug Act* to include a statutory definition of "medical food." The term *medical food*, as defined in section 5(b) of the *Orphan Drug Act* (21 U.S.C. 360ee (b) (3)) is:

> *"...a food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation."*

Medical foods are food, and therefore are regulated the same as foods. However, they cannot be marketed for a condition that can be managed or treated solely by a regular diet. That being said, any ingredient added to a medical food must be recognized as safe (GRAS). Medical foods do not need to be registered with the FDA, but the manufacturing facilities do for inspection purposes. Although they are not drugs, they still must meet the requirements for the manufacture and labeling of foods, which include CGMP regulations in manufacturing, packaging, and handling of human food. There is a particular compliance program for medical foods.

Go to FDA's Medical Food Guidances Q&A and answer the following questions: https://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ucm054048.htm

1. Does FDA regulation medical foods as drugs? Why/why not?
2. Do medical foods require clinical studies or premarket review (PMA)?
3. What labeling requirements apply to medical foods?
4. What is the purpose of FDA's compliance program for medical foods? There are three!
5. Do medical food require a prescription? Why/Why not?

VETERINARY PRODUCTS

The FDA has regulatory oversight over Animal & Veterinary Products. Veterinary products are a diverse area of regulation by the FDA and include animal drugs, biologics, food, medical feed, medical devices as well as grooming and pest control products. Because of this, the regulations and marketing approval that apply depend on the product itself. In this chapter, we briefly touch on some of the more prominent areas of veterinary products. For more information see the *Center for Veterinary Medicine (CVM)* as well as the USDA and EPA, all of which oversee the regulations of veterinary products.

Center for Veterinary Medicine, and (CVM): The CVM oversees regulation of food, food additives, drugs and biologics used on animals. They also conduct research that helps FDA ensure the safety of animal

drugs, food for animals, and food products made from animals. Here is a video on the CVM put out by the FDA. https://www.fda.gov/AboutFDA/CentersOffices/OfficeofFoods/CVM/ucm245225.htm

DRUGS FOR ANIMAL USE

The CVM regulates veterinary drugs under the authority of the Animal Drug Amendments to the *FD&C Act* (in 1968) in which provisions were added to ensure animal drugs, as well as human drugs, were safe and effective. Animal drugs must be produced under CGMP conditions outlined in 21 CFR 211. There are several central regulatory pathways for animal drugs; Investigational New Animal Drug (INAD), New Animal Drug Application (NADA), and Abbreviated New Animal Drug Application (ANADA).

New animal drugs are reviewed and approved through a pathway similar to human drugs. They first must get approval for clinical studies in animals through the INAD. To manufacture and sell a drug for use in animals the company must seek approval through a NADA. This application shows the drug has been tested in animal clinical studies and provides data demonstrating its safety and effectiveness. For generic animal drugs, again the process is similar to in humans, and the company must apply for an abbreviated application – ANADA – before marketing.

ANIMAL FOODS & FEEDS

Animal foods & feeds – such as a cat or dog food - as with human foods are covered by the *FFDCA* that require animal foods to be safe, wholesome and nutritious and are regulated by CVM. Additionally, canned pet foods have an obligation to follow canned food regulations in 21 CFR 113 ensuring pet food is free if viable microorganisms. For foods that are non-medicated do not require any pre-market approval but the ingredients do need to be GRAS and nutritious

Medicated foods, however, do require regulatory pathway depending on the class of medicated feed. Class A requires NADA (or ANADA), and Class B/C follow a unique route – Veterinary Feed Directive (VFD). VFD foods are available only under veterinarian supervision.

Let's Explore!

To learn more about the history and regulatory pathway of Pet foods, see FDA pet food resources page. https://www.fda.gov/AnimalVeterinary/ResourcesforYou/ucm047111.htm

OTHER CATEGORIES

Grooming devices are not regulated unless they show claims of therapeutic treatment. Medical devices for an animal are subject to regulation.

Veterinary biologics are licensed through USDA and Center for Veterinary Biologics (CVB) and are defined in the Virus-Serum-Toxin-Act (VSTA). These biologics follow the same regulatory and approval pathway as other animal drugs and must be safe and effective for the diagnosis, prevention, and treatment of animal diseases.

Pesticides for pets are regulated by EPA under FIRFA and includes topical flea treatments and insecticide dips – which intend to prevent, destroy, or repel pets externally. It is important to note that products for internal pests are treated as drugs. Pesticide regulation mainly focuses on safety to humans that handle the pets through or after treatment with pesticides including disposal.

THE REGULATORY OVERSIGHT OF COSMETICS

You might be surprised to learn that the FDA has regulatory oversight over cosmetics. You may be even more surprised to know that this oversight is largely self-regulated! The FDA takes action with hazardous products – but the remainder of the control is by the companies themselves. The other area the FDA does scrutinize heavily is misbranding. Many companies have recently moved to marketing their cosmetics with drug language – such as "anti-aging cream."

Some of the areas the FDA looks at when considering cosmetics is:

- ✓ regulations and policy governing the safety of cosmetic ingredients and finished products
- ✓ regulations, policy, and other activities dealing with proper labeling of cosmetics
- ✓ regulatory and research programs to address possible health risks associated with chemical or biological contaminants
- ✓ post-market surveillance and related compliance activities
- ✓ industry outreach and consumer education
- ✓ international standard-setting and harmonization efforts

As with foods, the complexity of the cosmetic industry and the technologies and ingredients used in the production of cosmetics is overwhelming. A global cosmetics industry has increased the calls for safety oversight since products and components enter the U.S. from many countries with different regulatory and safety standards. Some of the current areas of focus for cosmetics include:

- ➢ microbiological contaminants
- ➢ chemical contaminants
- ➢ drug vs. cosmetic products
- ➢ use of nanoscale materials as ingredients
- ➢ botanical ingredients
- ➢ alternatives to animal testing

WHAT IS A COSMETIC?

The Federal Food, Drug, and Cosmetic Act (FD&C Act) define cosmetics as *"articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body…for cleansing, beautifying, promoting attractiveness, or altering the appearance" (FDA.gov).* Lipstick, nail polish, moisturizers all are examples of cosmetics that would meet this definition.

The FDA excludes "soap" as a cosmetic – but this is a complicated and tricky topic. Soaps that are composed of fat and alkali (ex. Vegetable oil and lye) are not regulated at all by the FDA – but rather are under the purview of the Consumer Product Safety Commission. Soap that is advertised to cleanse, or beautify in any way, is regulated as a cosmetic. Moreover, soap that has a treatment claim, such as an anti-bacterial soap, is a drug! Whew!

IS IT A COSMETIC, DRUG OR BOTH?

One of the biggest issues with cosmetics is determining Is It a Cosmetic, a Drug, or Both? (Or Is It Soap?)
https://www.fda.gov/Cosmetics/GuidanceRegulation/LawsRegulations/ucm074201.htm
Whether a product is a cosmetic or drug primarily depends on its intended use. Different laws (above) come into play depending on what the use of the product. *A product can be considered both a cosmetic and drug when it is used to diagnose or treat a disease or disorder and to beautify*. An excellent example of this would be dandruff shampoo – it is used to both clean the hair as well as treat a disorder. Ultimately, which regulations apply depend on labeling and marketing.

LAWS & REGULATIONS PERTAINING TO COSMETICS

Many laws and regulations pertaining to the regulatory affairs of cosmetics. To learn more click on the law below!

- Federal Food, Drug, and Cosmetic Act
- Fair Packaging and Labeling Act
- Regulations Related to Cosmetics, Title 21, Code of Federal Regulations
- Key Legal Concepts: Interstate Commerce, Adulterated, and Misbranded
- Prohibited & Restricted Ingredients
- Color Additives Permitted for Use in Cosmetics
- FDA Authority Over Cosmetics
- View More Resources on Laws & Regulations

GOOD MANUFACTURING PRACTICE FOR COSMETICS

The FDA provides CGMPs for cosmetic products – however, there are no requirements in the *FD&C Act* for cosmetic products to be manufactured under CGMPs. Many legislative attempts have been made to change this, but so far, none has passed. The industry does provide many of its manufacturing guidelines; some follow the international Guidances provided in ISO 22716.
https://www.fda.gov/Cosmetics/GuidanceRegulation/GuidanceDocuments/ucm2005190.htm

ADULTERATION OF COSMETICS

One of the FDA enforcement areas is of facility and product inspection. Specifically, the FDA is looking for:

- Poisonous or deleterious substance that may injure the customer under regular use
- Filthy, putrid or decomposed substance (including microorganism contamination)
- Packaging under unsanitary conditions
- The container is composed of poisonous or deleterious substance
- Product contains unsafe (or unapproved) color additive
- Any outlawed ingredient (ex. Mercury, lead, zirconium, chlorofluorocarbons)
- Prohibited cattle material (brain, skull, spinal cord)

FDA's ENFORCEMENT TOOLS FOR FOOD & COSMETIC PRODUCTS

In the next chapter, we will discuss FDA enforcement tools. Briefly, for food & cosmetics, the FDA focuses its enforcement on:

- ✓ inspection of establishments
- ✓ collection and analysis of samples
- ✓ monitoring of imports
- ✓ monitoring of adverse event reports and consumer complaints
- ✓ premarket review (e.g., food and color additives)
- ✓ notification programs (e.g., food contact substances, infant formula)
- ✓ regulations/agreements (e.g., memoranda of understanding)
- ✓ consumer studies focus groups
- ✓ laboratory research
- ✓ develop/improve methods for detecting pathogens and chemical contaminants
- ✓ determine health effects of food and cosmetic contaminants
- ✓ determine effects of processing on food composition and allergenicity
- ✓ determine health effects of dietary factors
- ✓ determine skin penetration of cosmetic ingredients and contaminants

Summary

- ✓ The FDA (through CFSAN) has regulatory authority over food which includes recall authority thanks to FSMA
- ✓ The regulation of foods containing GMOs is overseen by three government agencies; the FDA evaluations food and feed safety, the USDA ensures agricultural safety and the EPA which ensures environmental safety
- ✓ Medical foods are distinguished from other foods in that they are specially formulated for particular dietary uses – however, since they are not a drug they do not need a prescription or go through a regulatory pathway
- ✓ Any ingredient in food must be GRAS
- ✓ Veterinary products are overseen by the CVM which include food, drugs, and medical devices for animals
- ✓ Animal drugs must go through INAD or ANADA before marketing
- ✓ The FDA has regulatory oversight over cosmetics and focuses their attention mainly on hazardous products and misbranding
- ✓ Cosmetics with treatment claims are classified as drugs

CHAPTER 10: FDA ENFORCEMENT

Objectives

- ✓ Identify FDA monitoring & enforcement practices and where they obtain regulatory authority to do so.
- ✓ Understand enforcement terminologies such as misbranding, adulteration, recall, inspection, injunction, and debarment.
- ✓ Explore the civil and criminal enforcement tools at the FDA's disposal: seizure, injunction, warning letters, 483, recall, debarments, civil money penalty, and criminal enforcement. Understand the relative harshness of these tools.
- ✓ Know the limitations to the FDA monitoring and enforcement; recall authority, criminal prosecution.
- ✓ Find warning letters, 483s, press releases, and recall notices at the FDA
- ✓ Distinguish between the products the FDA has recall authority over and the ones they do not. Apply an understanding of class I, II, & III recalls.

FDA MONITORING AND ENFORCEMENT

You have explored how the FDA is organized, the Centers overseeing different products, and dove into some of the product areas themselves. Next, we will examine the regulations that govern this process and how the FDA inspects and enforces laws in this area to protect public health. The FDA is mandated by the *FD&C Act* to protect the public health from adulterated and misbranded regulated products and has significant and broad enforcement power to do so. FDA has the authority to not only enforce the laws but also communicate regulations in the *Code of Federal Regulations, under Title 21*. Companies are highly encouraged to engage the FDA in all forms of communication as these communication methods serve as a prior notice of a lawsuit. However, aside from lawsuits, or regulations where the FDA has recall authority, most communication responses from the company are voluntary.

FD&C Act SECTION 331

The list of prohibited acts in which the FDA may pursue action against a company for is outlined in the *FD&C Act Section 331*. These all apply as long as the product is regulated by the FDA; biologics, drugs, devices, cosmetics, etc. Below are some key areas of the Act as they relate to enforcement. You will notice that it makes companies responsible for adulteration, even for outside third party vendors. Since regulations are continually evolving based on new or changing laws, and needs of the public, the FDA distributes an annual report to help the public make sense of current regulations.
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm090410.htm

LEGAL TERMINOLOGY

Before we continue on the discussion of FDA enforcement, it is important to understand some key terms in this area. The *FD&C Act* frequently refers to interstate commerce, adulteration and misbranding.
https://www.fda.gov/cosmetics/guidanceregulation/lawsregulations/ucm074248.htm

What the FD&C Act Means by "Interstate Commerce." "Interstate commerce" applies to all steps in the manufacture, packaging, and distribution of a product. It is common that some of the ingredients or packagings most likely originate from out of state, or even out of the country and even will leave the state.

What Makes a Product Adulterated?

From the FDA (FDA, 2016) *"A product shall be deemed to be adulterated if:*

- ✓ *If it bears or contains any poisonous or deleterious substance which may render it injurious to users under the conditions of use prescribed in the labeling*
- ✓ *If it consists of any filthy, putrid, or decomposed substance.*
- ✓ *If it has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health.*
- ✓ *If its container is composed of any poisonous or deleterious substance which may render the contents injurious to health.*
- ✓ *If it contains an unapproved color (or other) ingredient."*

Note that in regards to adulteration the law addresses the composition of the product, the conditions under which the product is manufactured, shipped, and stored, the product's container.

What makes a product Misbranded?

Section 602 of the *FD&C Act* [21 U.S.C. 362] describes what causes a product to be considered misbranded. It includes not only what the label says but also what it fails to say! "A product shall be deemed to be misbranded:

(a) If its' labeling is false or misleading

(b) "If the label is missing (1) the name and place of business of the manufacturer, packer, or distributor; and (2) an accurate statement of the quantity of the contents in terms of weight, measure, or numerical count: Provided, That under clause (2) of this paragraph reasonable variations shall be permitted, and exemptions as to small packages shall be established, by regulations prescribed by the Secretary" (FDA.gov).

(c) If any word, statement, or other information required by or under authority of this Act to appear on the label or labeling is not prominently placed

(d) If its container is so made, formed, or filled as to be misleading.

Note that under the *FD&C Act*, the term "misbranding" applies to:

- ✓ False or misleading information
- ✓ Lack of required information
- ✓ Conspicuousness and readability of required information
- ✓ Misleading packaging
- ✓ Improper packaging and labeling
- ✓ Deficiencies where the Poison Prevention Packaging Act requires special packaging.

Labeling regulations are very complex and are unique to the product. See the appropriate CFR or labeling information on the FDA website for details.

Some critical areas in the FD&C Act Section 331 as they relate to enforcement:

- ➢ *"The introduction or delivery for introduction into interstate commerce of any food, drug, device, or cosmetic that is adulterated or misbranded" [FD&C Act, sec. 301(a); 21 U.S.C. 331(a)].*
- ➢ *"The adulteration or misbranding of any food, drug, device or cosmetic in interstate commerce" [FD&C Act, sec. 301(b); 21 U.S.C. 331(b)].*
- ➢ *"The receipt in interstate commerce of any food, drug, device, or cosmetic that is adulterated or misbranded, and the delivery or proffered delivery thereof for pay or otherwise"[FD&C Act, sec. 301(c); 21 U.S.C. 331(c)].*
- ➢ *"The alteration, mutilation, destruction, obliteration, or removal of the whole or any part of the labeling of, or the doing of any other act with respect to, a food, drug, device, or cosmetic, if such act is done while such article is held for sale (whether or not the first sale) after shipment in interstate commerce and results in such article being adulterated or misbranded" [FD&C Act, sec. 301(k); 21 U.S.C. 331(k)].*

Here are some of the common violations of the FD&C Act:

- Adulterated or misbranded regulated product
- Receiving or delivering adulterated or misbranded product
- Refusal for inspection
- Counterfeiting product
- Altering product label
- Not registering a product
- Refusal to provide required documents

MONITORING

Bioresearch Monitoring. "The overarching goals of the FDA's bioresearch monitoring (BIMO) program, are to defend the rights, safety, and welfare of subjects involved in FDA-regulated clinical trials" (fda.gov). https://www.fda.gov/ICECI/EnforcementActions/BioresearchMonitoring/default.htm. Additionally, the BIMO serves to determine the accuracy and reliability of clinical trial data submitted to FDA and to assess compliance with FDA's regulations governing the conduct of clinical trials. The BIMO program performs on-site inspections of both clinical and nonclinical studies carried out to support research and marketing applications/submissions to the agency.

The FDA Tests Products. How do quality issues come to the attention of the FDA? The FDA can purchase and test products on its own. The FDA can also inspect production facilities. If a product is found to be defective (or an inspection facility to be out of compliance), there are several options the FDA may pursue: 1. warn the public, 2. seize products from the market, and 3. bring a seizure or injunction case in court, to name a few.

INSPECTIONS

The FDA has the legal authority to inspect pharmaceutical companies, and it can do so unannounced. The guidelines to the inspections can be found at the Inspections, Compliance, Enforcement, and Criminal Investigation (ICECI) webpage. Different inspection guidelines govern different product types.

The FDA performs routine (every two years) inspections for compliance with CGMP, GLP, GCP and Quality System Regulations. They also perform targeted inspections based on other enforcement events such as follow-ups on recall events or warning letters. When the FDA enters a facility for inspection, they provide the inspection request document (FDA 482) as well as provide identification. If they are refused entry, the FDA can obtain a search warrant from a federal court. The scope of the inspection is primarily based on the reason for the visit and the history of the facility. The only limits the FDA has in inspections relates to financial information, sales data (not related to shipping), personnel data (not related to training) and research data (not related to approval of products).

During inspections, the FDA looks at seven system to determine if they are 'in control':

- ✓ management responsibility
- ✓ Design control
- ✓ Corrective and preventative action (CAPA)
- ✓ Production and process controls
- ✓ Records and document change controls
- ✓ Material controls
- ✓ Facilities and equipment controls

FORM 483

Adulteration and misbranding are the two most common violations found during an inspection. Pharmaceutical facilities and biotechnology companies are periodically inspected by the FDA. *Any CGMP violations the inspectors find are noted on forms, called "483's" and if no response to the regulatory compliance issues, an official Warning Letter is sent to the company.*

A 483 is a result of an inspection and notice of regulatory non-compliance. It is a list of specific items seen at the end of the inspection and is issued by the investigator. After an inspection, the inspector meets with the facilities manager to address as many of the problems before the 483 is written. The inspector offers an opportunity to remedy a situation immediately after the inspection and document compliance and remedies, or future solutions and agreements. After the letter is written and received by the company, the company then has 15 working days to voluntarily respond to the 483 in writing with an action plan. If the 483 issued is not remedied quickly, the FDA can then respond with a warning letter (see below).

It should be noted that issuance of form 483 does not automatically mean that a drug firm is not in GMP compliance. Additionally, the length of the form is not a reliable indicator of the seriousness of any observed violations. The form should be viewed critically, and companies that feel they have received a 483 containing questionable observations of GMP deviations should discuss the issue with the inspector, district director, regional director or even the center of issuance if necessary.

All form 483s are posted on the FDA website:
http://www.fda.gov/AboutFDA/CentersOffices/ORA/ORAElectronicReadingRoom/default.htm

Companies are not required to respond to a 483. However, their response is recommended. If a company receives too many 483s and are not providing the FDA with adequate responses to these forms, they are subjected to a warning letter or more punitive measures as outlined below.

ESTABLISHMENT OF INSPECTION REPORTS

After the FDA closes an inspection, they release an Establishment of Inspection Report (EIR). It is a formal written report summarizing the findings with supporting evidence. In this report, the FDA classifies the inspection as No Action Indicated (NAI), Voluntary Action Indication (VAI), or Official Action Indicated (OAI). If an OAI is noted, enforcement activities may be listed or be scheduled to come.

ENFORCEMENT ACTIVITIES - CIVIL ENFORCEMENT

Regulations must be enforceable to be effective, and the FDA has plenty of tools to encourage compliance. The key for the FDA is product public health and safety. Enforcement proceedings usually take place after an inspection has been deemed OAI. The inspections, through appropriate centers, can be either every two years or as indicated by an issue the FDA has been made aware. There are two broad categories of enforcement activities; civil and criminal.

The guidelines to the enforcement actions the FDA takes can be found at the Inspections, Compliance, Enforcement, and Criminal Investigation (ICECI) webpage. The FDA publishes enforcement activities in annual reports to their website. Look around and see what kinds of enforcement activities are most prominent.

WARNING LETTERS

A warning letter issued by the FDA is a voluntary compliance letter outlining the issues of regulatory significance resulting from the inspection. The warning letter offers a company the opportunity to remedy the regulatory situation - it is an informal and advisory communication. *The overall goal of a warning letter*

is to encourage voluntary compliance. If the issue does not put the public in immediate danger, a warning letter may be written before other punitive measures. A warning letter allows companies an opportunity to make voluntary corrections to compliance matters by letting them know there's an issue. The second and equally important reason for warning letters is to establish a record of 'prior notice' during legal proceedings. However, when issued, a warning letter is published immediately on the FDA website and is shared across regulatory agencies.

FDA Enforcement Statistics
Summary
Fiscal Year 2016

Enforcement Type	FY16 Summary Numbers
Seizures	4
Injunctions	17
Warning Letters	14590
Recall Events	2847
Recalled Products	8305
Drug Product Debarments	1
Food Importation Debarments	0

FDA Enforcement Statistics summary, 2016.

OTHER CORRESPONDENCE

Untitled Letters. Untitled letters are the least harsh form of communication with the FDA. Similar to Warning Letters, the untitled letters can notify a company of a violation that may not reach the threshold of a regulatory issue. It does not give warnings. However, companies are encouraged to address any issues as this does constitute 'prior notification,' and is why you should respond.

Press Release. "The FDA can also issue unfavorable press releases or federal register notices. In the event of an egregious defect, the FDA can criminally prosecute, seize materials, and perform injunctions against a company and individuals." (fda.gov) https://www.fda.gov/ICECI/CriminalInvestigations/ucm123086.htm

Let's Explore!

Read this article:http://www.fda.gov/AboutFDA/Transparency/Basics/ucm194988.htm

a. Why isn't a drug taken off the market when a company receives a warning letter?
b. What are some repercussions that a drug manufacturer faces if they choose to ignore the warning letter?

RECALLS – Drugs, Devices & Food

The FDA can only issue a recall when they have the mandated power to do so. The FDA cannot recall a drug, or biologic, but can recall a medical device, some cosmetics, and food. When they do have recall authority, they can only do so when there is a substantial public health and safety risk.

Drug. *The FDA cannot force a company to recall a drug*, but companies will usually recall voluntarily or at the request of the FDA.

Food. *The FDA can issue a food recall*. In 2011, the FDA gained increased authority in regulating and responding to food product contamination via the new *Food Safety Modernization Act (FSMA)*. The FSMA allows the FDA to suspend the services and production of food distributors if contamination is suspected. There need not be any proof of the source of the contamination. For more information on the FSMA: http://www.foodsafety.gov/news/fsma.html

Medical Device. *The FDA can issue a device recall*. In 2012, the US Food and Drug Administration (FDA) announced that it was seeking to implement medical device recall authority under § 518(e) of the *FD&C Act* and Chapter 21, Section 810 of the CFR. Recall authority for medical devices would permit the FDA to order manufacturers to cease distribution of a device and notify health professionals if FDA finds a "reasonable probability that the device intended for human use would cause serious adverse health reactions or death." (fda.gov) *A medical device recall is an action that takes place to address a problem with a medical device that may be in violation of an FDA law.* Recalls occur when the device is defective, a risk to health, or both. A recall does not necessarily mean the product must be returned, sometimes it just needs to be adjusted, or clarification safety instructions provided. 21 CFR 7 provides Guidances for conducting an efficient voluntary recall.

Examples of the types of actions that may be considered recalls:

- ✓ Inspecting the device for problems
- ✓ Repairing the device
- ✓ Adjusting settings on the device
- ✓ Re-labeling the device
- ✓ Destroying device
- ✓ Notifying patients of a problem
- ✓ Monitoring patients for health issues

A medical device recall is either a correction or a removal. A Correction addresses a problem with a medical device in the place where it is sold. A Removal approaches the problem by removing the device from where it is sold. *In most cases, a company voluntarily recalls a device on its own.* When the company has violated an FDA law, the company must recall the device (correction or removal) and notify the FDA. *Legally, the FDA can require a company to recall a device if an organization refuses to do so under 21 CFR 810, Medical Device Recall Authority.* 21 CFR 810 describes the procedures the FDA follows in exercising its medical device recall authority under section 518(e) of the FD&C Act.

It should be noted, "A recall does not include a market withdrawal or a stock recovery. A market withdrawal is a firm's removal or correction of a distributed product which involves a minor violation that would not be subject to legal action by the FDA or which involves no violation, e.g., normal stock rotation practices, routine equipment adjustments and repairs, etc." (fda.gov). In the end, almost all recalls are conducted on a voluntary basis by the manufacturer.

A comprehensive searchable recall device database is found here.
https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRES/res.cfm

Device recalls following the same general recall procedure as previously discussed for drugs. This includes classification of recall (I, II or III) developing a recall strategy and providing the FDA with recall status reports. To learn more about Device Recalls, visit the FDA device recall web page https://www.fda.gov/medicaldevices/safety/listofrecalls/ and also, watch the FDA Video here.
http://fda.yorkcast.com/webcast/Play/1b95461f64be40ecbe3415195cb3949 11d

CASE STUDY: Tylenol versus the FDA

Consumer complaints of an "unusual moldy, musty or mildew-like" odor prompted Tylenol to announce a broad-based recall in 2010 of Tylenol, Motrin, Benadryl and other drugs. The issue first became known in 2008, but the company ignored it. This prompted the FDA to send Johnson & Johnson (the makers of Tylenol) scathing inspected and warning letters for not reacting quickly to the problem.

The initial Form 483

The initial warning letter

In September of 2010, the Principal Deputy Commissioner of the FDA made a statement before the Committee on Oversight discussing the serious quality lapses at two McNeil (Johnson & Johnson) production facilities, which led to numerous recalls of over-the-counter (OTC) medications. The FDA testified "since it has no legal authority to require a manufacturer to recall a drug product the recall system depends on full and open disclosure, trust, and the industry's acceptance of its responsibilities to protect the public from adulterated products" (oversight.house.gov). Johnson & Johnson abused that trust which resulted in adulterated products being left on the shelves longer than they needed to be. The FDA argued that if they had the authority simply to order a recall, these events would not have occurred, and the products would have been removed from the shelves faster resulting in fewer people being affected by these products.

a. What were the three violations the company was cited? Why does the FDA care about these particular violations?
b. What are the potential outcomes if the manufacturer does not comply and address the FDA's citing?
c. Do you think the FDA should have recall authority over drugs as they do medical devices?

Class I, II & III Recalls

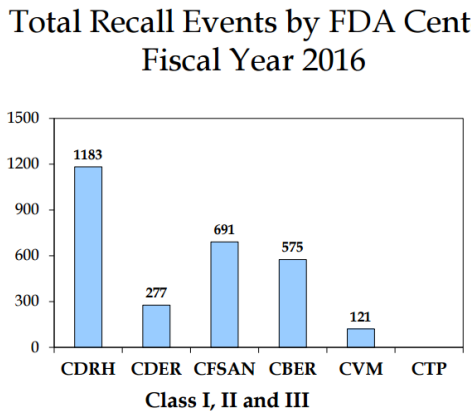
- Class I Recall: "A reasonable probability that the use of or exposure to a violative product will cause serious adverse health consequences or death." (fda.gov)
- Class II Recall: "use of or exposure to a violative product may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote." (fda.gov)
- Class III Recall: "use of or exposure to a violative product is not likely to cause adverse health consequences." (fda.gov)

Read the article and watch the video "FDA 101: Product Recalls - From First Alert to Effectiveness Checks" and read FDA FAQs here. Here is an informative video on how FDA handles recalls: http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm182929.htm https://www.fda.gov/ForConsumers/ConsumerUpdates/ucm049070.htm

a. How does the FDA first learn about a problem with a product?
b. How does the FDA alert the product about a product recall?
c. Discuss an example of a recall, and state what class of recall it is and why.

"Market withdrawal occurs when a product has a minor violation that would not be subject to FDA legal action. The firm removes the product from the market or corrects the violation. For example, a product removed from the market due to tampering, without evidence of manufacturing or distribution problems would be a market withdrawal." (fda.gov)

"Medical device safety alert: issued in situations where a medical device may present an unreasonable risk of substantial harm. In some case, these situations also are considered recalls." (fda.gov) The FDA Drug Safety Podcasts are produced by FDA's CDER and provide emerging safety information about drugs in conjunction with the release of Public Health Advisories and other drug safety issues." (fda.gov) https://www.fda.gov/Drugs/DrugSafety/DrugSafetyPodcasts/default.htm



FDA Enforcement Statistics summary, 2016.

SEIZURES

If a company refuses to recall, the FDA can bring a seizure or injunction case against it to address violations even if the products are not defective. Then, they can petition the court for an order that allows federal officials to take possession of "adulterated" drugs and destroy them. This process enables the FDA to immediately prevent a company from distributing defective and potentially harmful drugs to consumers. *Both seizure and injunction cases frequently result in court orders that require companies to take many steps to correct violations*. These steps may include hiring outside experts to help resolve the problem, writing new procedures and training employees. In some cases, violations may become criminal cases, allowing the FDA to seek fines and jail time.

INJUNCTIONS

If a company violates the *FD&C Act*, the FDA may file an injunction against the company. This injunction is a civil judicial proceeding and is typically used when a significant health hazard is identified with a product. This FDA may seek a temporary restraining order, a temporary injunction or permanent injunction. The key here is for the FDA to be able to act quickly to get a product to stop from reaching the customers short of a recall (which the FDA does not have authority in some cases). The FDA also uses this enforcement method if the company has ignored repeated warning letters. If the company addresses the issues, the temporary restraining order can be lifted.

CIVIL MONEY PENALTIES

The *FD&C Act*, as well as the *PHSA*, have civil money penalty provisions. Guidance on CMP is provided in 21 CFR 17.2. Look up the CFR on the FDA website, and notice the CMPs are quite harsh! Some penalties exceed a million dollars for aggregate offenses.

DISQUALIFICATION OF CLINICAL INVESTIGATORS

The FDA can disqualify a clinical investigator and prevent them from providing any clinical data for any product submission. Typically, information on clinical investigators is obtained through the BIMO inspection.

DEBARMENT

The FDA has debarment authority of individuals or companies from the drug industry. Debarment means they are banned and can no longer work for anyone manufacturing an approved drug. Debarred companies can no longer manufacture, nor submit any further drug applications. Debarred people can also be subject to civil money penalties as well! See a list of debarments on FDA website. You will notice it is a shockingly long list! https://www.fda.gov/ICECI/EnforcementActions/FDADebarmentList/default.htm

CRIMINAL ENFORCEMENT

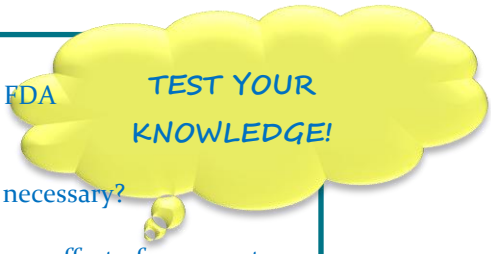
Criminal investigations are made by the Office of Criminal Investigations (OCI). It is important to remember when we are discussing FDA regulations on Food & Drugs we are referring to laws. Breaking laws have many penalties, which can range from fines to injunctions to jail time!
https://www.fda.gov/ICECI/CriminalInvestigations/default.htm

Read here a featured story on the OCI website: *"April 4, 2016: Former Carlsbad Resident Jailed for Sale of Unapproved "Energy Wave" Medical Devices."*
https://www.fda.gov/ICECI/CriminalInvestigations/ucm494563.htm

a. *What is David Perez accused of doing?*
b. *Why is this against the law? Can you reference the law?*
c. *How long of a sentence did he receive? If he did not receive a plea deal and was found guilty in a court of law, how long would his maximum sentence have been?*
d. *Do you agree with the charge and his sentence? Explain.*

Consent Decree

Companies that repeatedly violate CGMP requirements may be forced to make changes via the issuance of a consent decree. T*he consent decree is signed by the company's top official, the U.S. Attorney, and the U.S. District Court.* The decree is then filed with the court and is later submitted to the FDA. Enforced by the Federal courts, consent decrees typically involves fines, reimbursements to the government for inspection costs, and penalties for noncompliance. Consent decrees can be permanent, however, if a company has complied, it can petition the court to remove the decree.



Go to: http://www.CGMP.com/consentDecree.htm and http://www.fda.gov/ICECI/Inspections/IOM/ucm122512.htm#SUB2.4 to review FDA procedures on Consent Decrees.

a. What prior action does the FDA take before a consent decree becomes necessary?
b. Who signs a consent decree?
c. What is the adverse effect of consent decrees on FDA? What is the adverse effect of a consent decree on the company?

Summary

- ✓ The FDA is mandated by the *FD&C Act* to protect the public health from adulterated and misbranded regulated products and has significant and broad civil and criminal enforcement power to do so
- ✓ FDA has the authority to not only enforce the laws but also communicate regulations in the *Code of Federal Regulations, under Title 21*
- ✓ The FDA has the legal authority to inspect companies and can do so unannounced
- ✓ Violations found during an inspection are outlined in either a untitled letter, warning letter and a 483 depending on the severity, and history of the violation
- ✓ Companies are not required to respond to these communications but are encouraged to do so
- ✓ The FDA has recall authority over medical devices and food, but not drugs
- ✓ The FDA could seize products if a company refused to comply with a mandatory or voluntary recall
- ✓ A company may file an injunction on a business that may result in a product being destroyed
- ✓ The FDA can penalize egregious violations with civil money penalties, disqualification of clinical investigators, disbarment from the industry altogether and even imprisonment

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