

Steps to a Quality CBER Submission

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Quality

- **“Quality is never an accident; it is always the result of intelligent effort.” John Ruskin**
- **“If you can't describe what you are doing as a process, you don't know what you're doing.” W. Edward Deming**

Outline

- ❑ CBER overview, products, review process
- ❑ Resources
- ❑ Statutes and Regulations
- ❑ Recommendations BLA and Supplements
- ❑ Problems During Review
- ❑ Problems During Inspection
- ❑ Summary

**“If men were angels,
no government would be
necessary”**

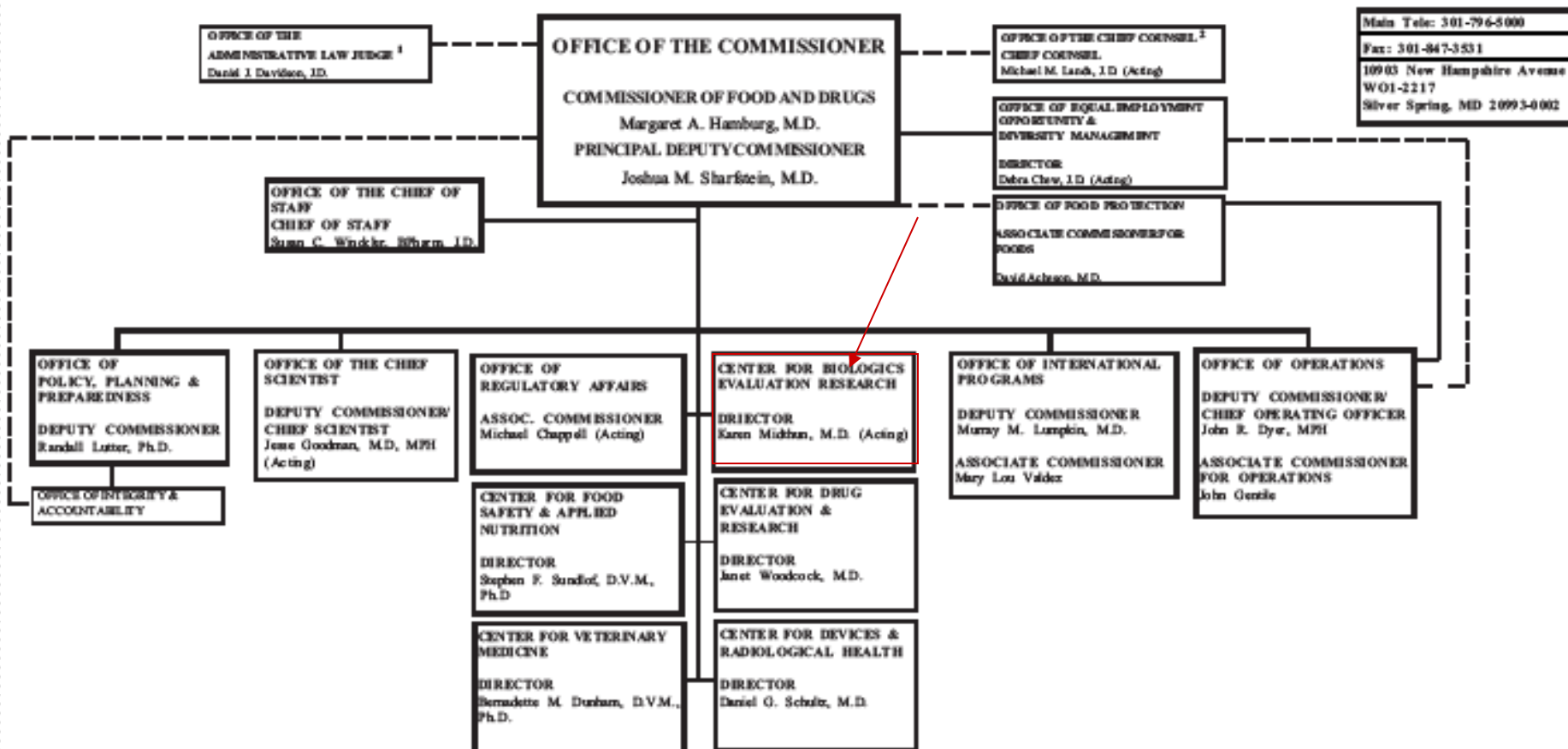


**President James Madison,
Federalist Papers**

STEP 1

BE FAMILIAR WITH FDA -
WHAT DO THEY DO?
WHAT'S THEIR PURPOSE?

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION



Main Tele: 301-796-5000
Fax: 301-847-3531
10903 New Hampshire Avenue
W01-2217
Silver Spring, MD 20993-0002

¹Reports Directly to the Secretary, HHS

²Reports to the General Counsel of the HHS, and advises the Commissioner of Food and Drugs.

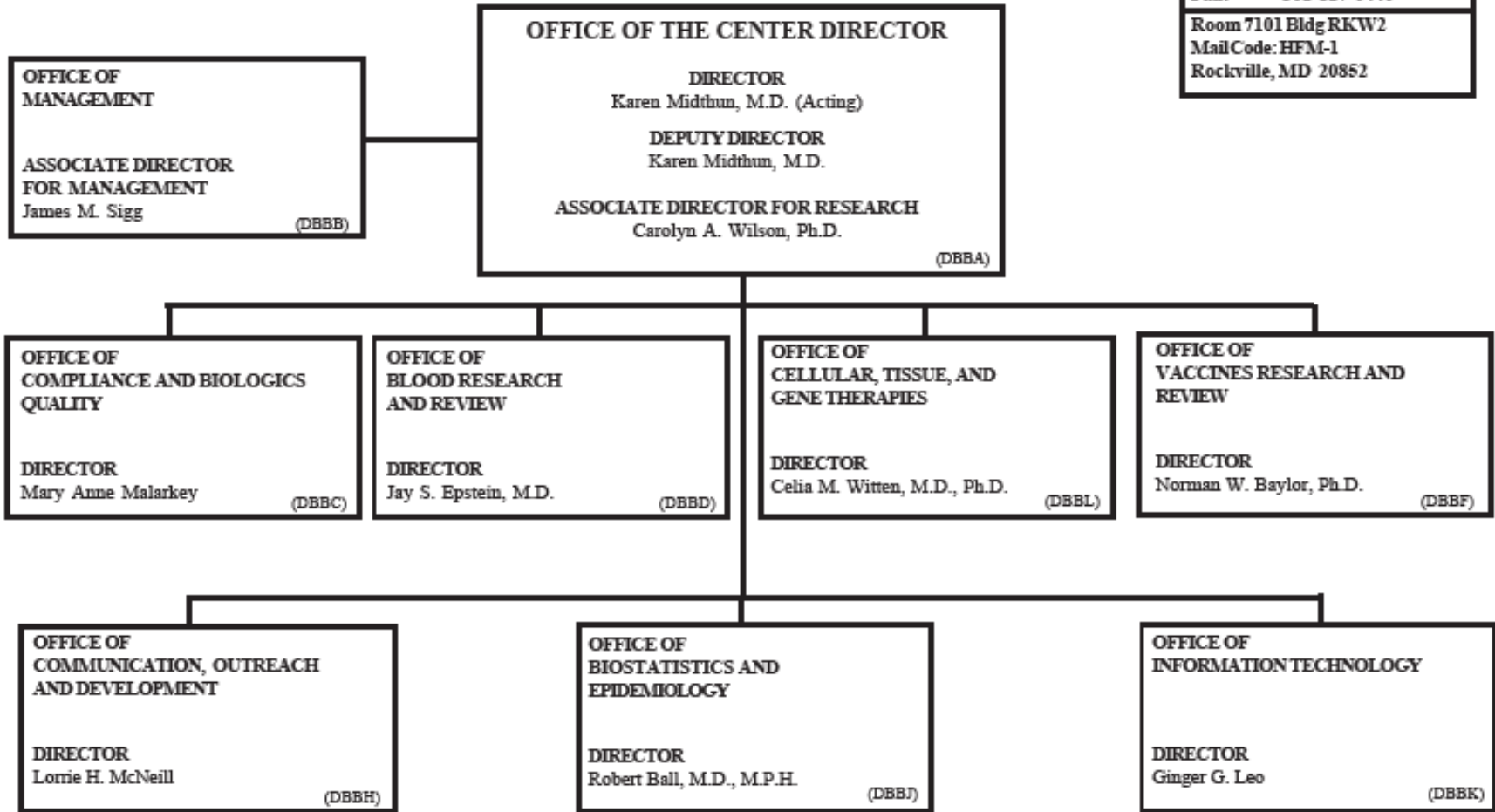


What We Do - FDA Mission

- ❑ WE protect the public health by assuring safety and efficacy of regulated products
- ❑ WE regulate human and veterinary drugs, medical devices, the food supply, cosmetics, products that emit radiation
- ❑ WE advance public health by helping speed innovations making medicines and foods more effective, safer, and more affordable
- ❑ WE help the public get accurate, science-based information to use medicines and foods to improve their health.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

Main Tel: 301-827-0372
Fax: 301-827-0440
Room 7101 Bldg RKW2 Mail Code: HFM-1 Rockville, MD 20852

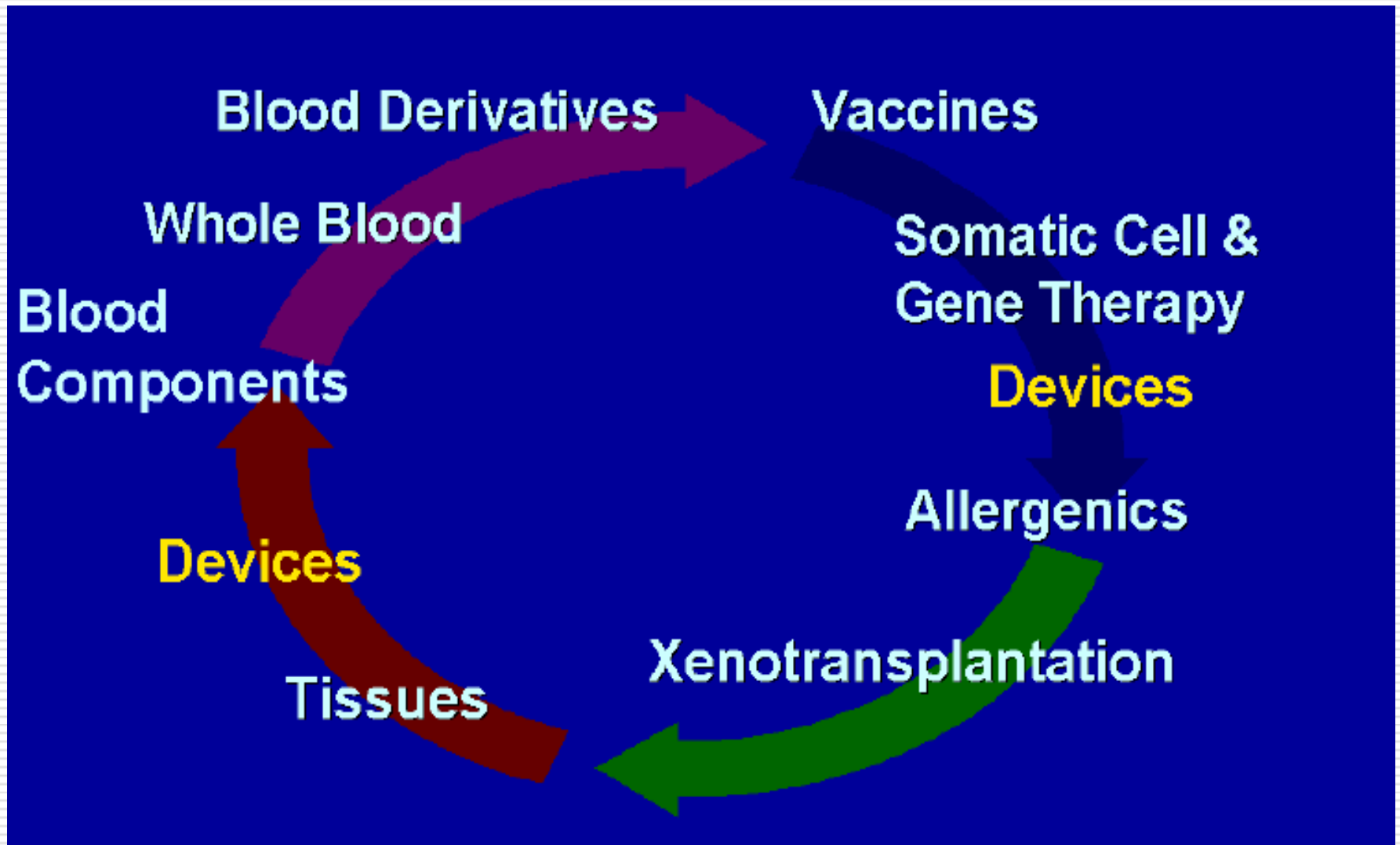




What We Do - CBER Mission

- ❑ WE ensure the safety, purity, potency, and effectiveness of biological products
 - ❑ WE regulate vaccines, blood and blood products, recombinant products, cells tissues and gene therapies, and medical devices for the prevention, diagnosis, and treatment of human diseases, conditions, or injury
 - ❑ WE help to defend the public against the threats of emerging infectious diseases and bioterrorism
-

Overview - CBER Products



Overview

CDER Submission Types

- ❑ IND, IDE, Master Files
- ❑ **Biologic License Applications (BLA) and supplements biologic drugs**
- ❑ **BLA in-vitro diagnostics related to blood transfusion (blood grouping reagent, HIV, hepatitis, Chagas, West Nile test kits)**
- ❑ PMA and 510(k) devices related to blood transfusion or cell and gene therapy
- ❑ NDA & ANDA Plasma volume expanders (dextran 40, dextran 70, hetastarch, pentastarch)
- ❑ NDA & ANDA anticoagulants (citrate phosphate, citrate dextrose, heparin, urokinase)

Overview

CBER Review Team

- ❑ Regulatory Project Manager
- ❑ Clinical reviewer
- ❑ Toxicologist
- ❑ Product / CMC reviewers
- ❑ Statistician
- ❑ Bioresearch monitoring reviewer
- ❑ **Facility / CMC reviewer, inspector**
- ❑ Lot testing and lot release reviewers
- ❑ Advertising and Promotional Labeling reviewer
- ❑ Information & electronic submission specialists
- ❑ Branch Chiefs, Division Directors, Office Directors

Overview

Steps of the Review Process

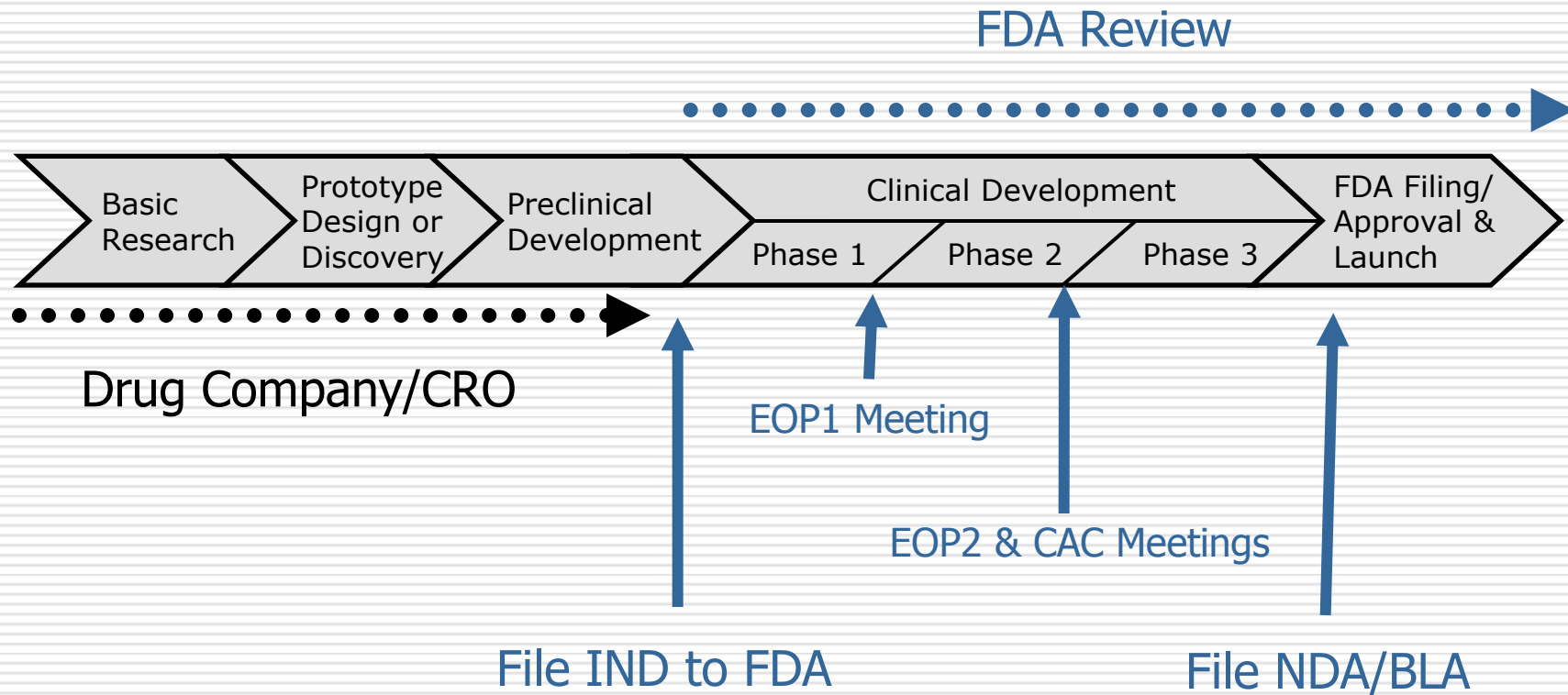
- ❑ Pre-Clinical
- ❑ IND – Phase 1
- ❑ IND – Phase 2
- ❑ IND – Phase 3
- ❑ **BLA - request for permission to introduce, or deliver for introduction, a biologic product into interstate commerce (21 CFR 601.2)**
- ❑ Post Marketing Phase 4
- ❑ **Supplements**, Annual Report, BPDR, Adverse Event Reporting

Overview

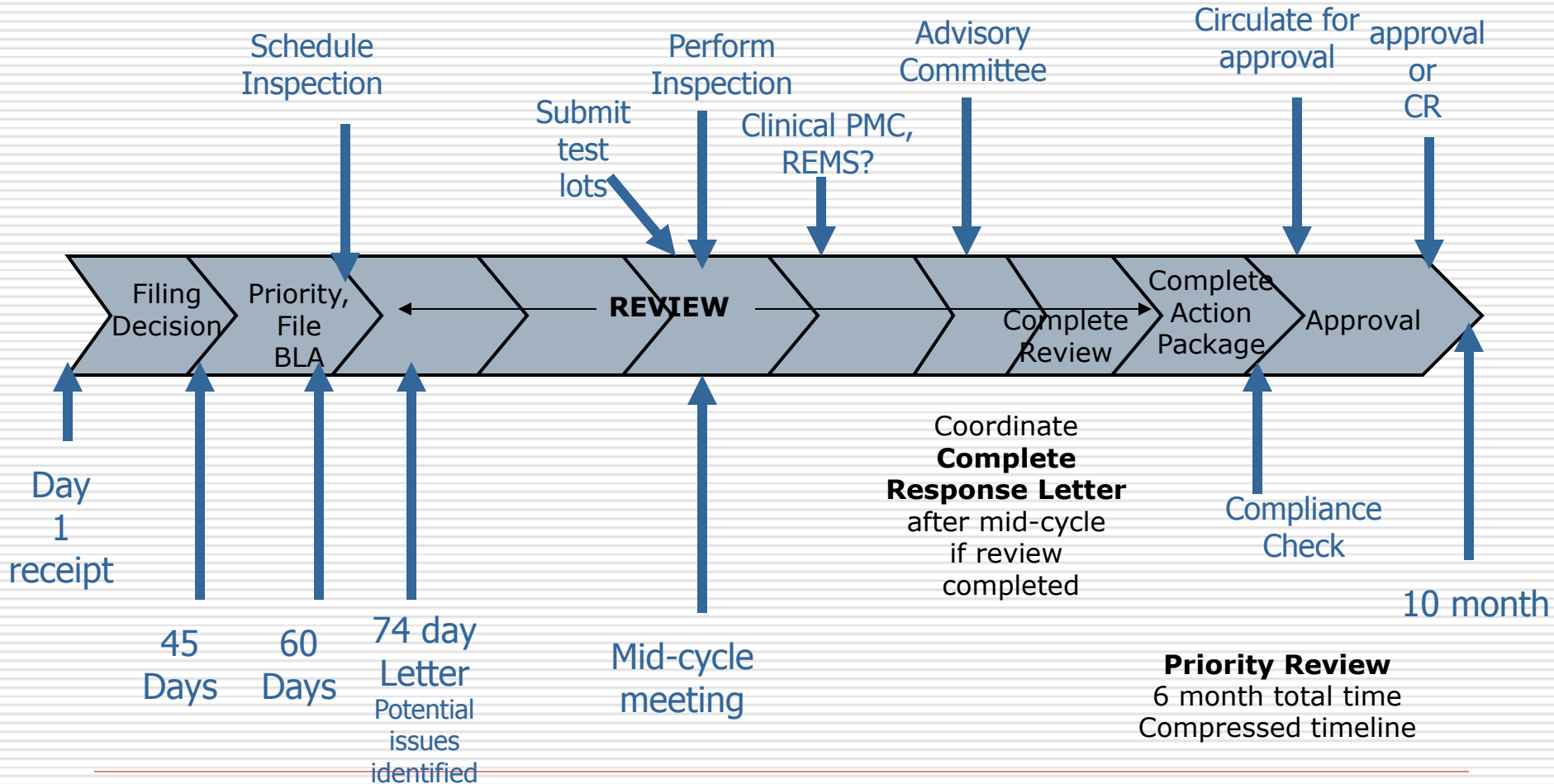
Review Process

- ❑ Review of most submissions must meet PDUFA or MDUFMA milestones
 - ❑ Initial review for filing (enough information submitted)
 - ❑ Review, information requests
 - ❑ Inspection – pre-license, pre-approval
 - ❑ Lot release
 - ❑ Complete response or approval
-

Overview of Drug Development



Overview of CBER BLA Review



STEP 2

KNOW YOUR STATUTES, REGULATIONS
and GUIDANCE

or

HOW CAN YOU MAINTAIN QUALITY AND
CONSISTENCY?

Resources

Biologic Statutes and Law

- History -
<http://www.fda.gov/AboutFDA/WhatWeDo/History/default.htm>
- Laws enforced by FDA -
<http://www.fda.gov/AboutFDA/WhatWeDo/Laws/default.htm>
- Federal Food, Drug & Cosmetic Act- 1938 laws gives FDA authority to oversee safety of food, drugs, cosmetics, devices, many amendments
- Public Health Service Act – 1944 is passed, covering broad spectrum of health concerns, including regulation of biological products and control of communicable diseases

Statute – Definitions

Section 201 FD&C Act

- (g)(1) The term "**drug**" means.....(B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; ...
- (h) The term "**device**" ... means an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is.....(2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or (3) intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.

Statute- What is Current Good Manufacturing Practice (CGMP)? – FD&C Act

- **SEC. 501. [21 USC §351] Adulterated Drugs and Devices**
A drug or device shall be deemed to be adulterated—
(a) (1) If it consists in whole or in part of any filthy, putrid, or decomposed substance; or **(2)**(A) if it has been prepared, packed, or held under insanitary conditions whereby it may have been contaminated with filth, or whereby it may have been rendered injurious to health; or **(B)** if it is a drug and the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with **current good manufacturing practice** to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess; ...

Statute – Inspection FD&C Act

- **Section 704, Factory Inspection** a) Right of agents to enter; scope of inspection; notice; promptness; exclusions. (1) For purposes of enforcement of this Act, officers or employees duly designated by the Secretary, upon presenting appropriate credentials and a written notice to the owner, operator, or agent in charge, are authorized (A) to enter, at reasonable times, any factory, warehouse, or establishment in which food, drugs, devices, or cosmetics are manufactured, processed, packed, or held, for introduction into interstate commerce or after such introduction, or to enter any vehicle being used to transport or hold such food, drugs, devices, or cosmetics in interstate commerce; and (B) to inspect, at reasonable times and within reasonable limits and in a reasonable manner, such factory, warehouse, establishment, or vehicle and all pertinent equipment, finished and unfinished materials, containers, and labeling therein.

Statute-Licensed Biologic Product

– PHS Act Section 351

- (i) Biologic product definition - A biological product is a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine or its derivatives (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.

Statute-Licensed Biologic Product – PHS Act Section 351

- (a) No person should introduce or deliver for introduction into interstate commerce any biological product unless... licensed and labeled
- (a)(3)(c)Any officer, agent, or employee of the Department of Health and Human Services, authorized by the Secretary for the purpose, may during all reasonable hours enter and inspect any establishment for the propagation or manufacture and preparation of any biological product.

Resources Regulations

- ❑ 21 CFR 312 Investigational New Drugs (INDs) 21 CFR 812 Investigational Device Exemptions (IDE), Drug Master Files (DMF) 21 CFR 314.420
- ❑ 21 CFR 600-680 relevant to biologics – licensing, manufacture, testing, and more
- ❑ 21 CFR 211 drug product - CGMP
- ❑ 21 CFR 820 finished device – QS Regulation
- ❑ 21 CFR 1271 human cell, tissue, cellular and tissue based products - CGTP

Resources Regulations

What to Submit?

- Sec. 601.2 Applications for biologics licenses; procedures for filing. (a) General. To obtain a biologics license under section 351 of the Public Health Service Act for any biological product, the manufacturer shall submit an application to the Director, Center for Biologics Evaluation and Research or the Director, Center for Drug Evaluation and Research (see mailing addresses in Sec. 600.2 of this chapter), on forms prescribed for such purposes, and shall submit

Resources

FDA and CBER Webpage

□ **FDA Webpage** <http://www.fda.gov/>

□ **CBER Webpage**

<http://www.fda.gov/BiologicsBloodVaccines/default.htm>

- Look under specific product type
- Development & approval process

Resources

FDA and CBER Webpage

□ **CBER Webpage**

- Guidance, compliance, & regulatory information
- News & events (presentations)
- Electronic submissions
<http://www.fda.gov/cber/esub/esub.htm>
- Links to approvals, warning letters, SOPs – tour the links

Resources

CBER Guidance Documents

- Guidance documents describe FDA's interpretation of or policy on a regulatory issue 21 CFR 10.115(b)
 - *Guidance for Industry for the Submission of Chemistry, Manufacturing, and Controls* information for appropriate product categories – these guidance provide you with a guideline of what a firm should submit for the CMC section, at the end of each document additional useful guidance

Resources

Guidance Documents

- CBER CMC documents for recombinant, vaccine, human or animal plasma derived, in-vitro diagnostic, allergenics, human blood and blood components, gene therapy INDs
- Guidance for Industry for the Submission Documentation for *Sterilization Process Validation* in Applications for Human and Veterinary Drug Products, November 1994

Resources

Guidance Documents

- Guidance for Industry Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice, September 2004
- Other guidance listed on the CBER website including ICH
- CDRH guidance that pertain to CBER devices
- Other applicable technical documents for biologics issued by USP and PDA
- Devices AAMI, ISO, ANSI, GHTF

Resources

Guidance Documents – Submission Format

- ❑ Electronic Submissions – ensure the submission is easy to navigate and all the links work - CALL or EMAIL FDA POC FOR HELP
- ❑ Electronic Submission Gateway (ESG)
- ❑ CTD format
<http://www.fda.gov/RegulatoryInformation/Guidances/ucm122049.htm>
- ❑ Non CTD format – based on 21 CFR 601.2, 21 CFR 314.50, CMC guidance

STEP 3

KNOW WHAT IS EXPECTED WHEN
YOU PREPARE A SUBMISSION

or

WHAT CAN I DO TO HAVE A QUALITY
SUBMISSION?

Recommendations

Submitting a BLA: Meetings

- ❑ Type A meeting necessary for an otherwise stalled drug development program to proceed
- ❑ Type B meetings include the following: Pre-IND, End of Phase 1, End of Phase 2/Pre-Phase 3, or a Pre-BLA/NDA meeting
- ❑ Type C meeting includes any other type meeting including cost recovery, general product issues, and facility issues with CBER/OCBQ/DMPQ regarding manufacturing facility end of Phase 2 or early Phase 3

Recommendations Before Submitting a BLA

- ❑ Reference the CMC guidance or ICH CTD guidance regarding what to submit
- ❑ Full scale manufacture consistency (conformance) lot data submitted with BLA
- ❑ Discuss with FDA how many consistency lots and lots on stability are needed prior to submission
- ❑ In-process and release specifications established and implemented

Recommendations Before Submitting a BLA

- ❑ Must manufacture using CGMP
- ❑ Batch records reflect current process
- ❑ Complete facility and equipment qualification, sign off on all documents
- ❑ Complete test method validation and process validation, sign off on all documents

Recommendations Before Submitting a BLA

- Quality unit implemented
- Container closure upstream and downstream
- SOPs reflect process for marketed product, reviewed and signed
- Deviations, non-conformities, and out of specifications tracked and investigated
- Corrective action & change control documented

Recommendations

Submitting a BLA

- ❑ Manufacturing facilities must be inspection ready and capable of manufacturing the product
- ❑ Facilities are registered including contract manufacturers and release test labs
- ❑ Communication - call and stay in contact with your FDA point of contact
- ❑ Request teleconferences with FDA if unclear about what to submit
- ❑ Request meetings (some limits) and resolve and address concerns that are identified

Recommendations After Approval Submitting a Supplement

- Supplements –
 - Cover letter describes entire change
 - What is the change to the product, equipment, and/or facility?
 - Why is the change taking place?
 - Where is the change occurring?
 - How was the change validated?

STEP 4

KNOW WHAT CAN BE AN
ADMINISTRATIVE OR DATA PROBLEM

Submission Problems - Administrative

- ❑ Electronic submissions are not formatted for easy navigation and referenced data is not linked
- ❑ Cover letters don't reflect what is in the submission, information is buried
- ❑ Protocols or validations submitted need to be summarized
- ❑ Previous plans or submissions are referenced but relevant information is not provided

Submission Problems - Administrative

- ❑ Submission is not stand alone
- ❑ Correct forms not submitted or not filled out correctly – for example 356(h) has no signature, facility listed, FEI number, or blank fields
- ❑ Submitted before complete to meet company deadlines
- ❑ Environmental assessment or categorical exclusion request not submitted or wrong category 21 CFR 25.40, 25.31

Submission Problems - Administrative

- ❑ Comparability protocols submitted with the BLA are not listed in cover letter, buried in the submission
- ❑ Contract manufacturing not described or not described in relation to BLA
- ❑ Colored coded flow diagrams are submitted in black and white
- ❑ Piping and Instrument diagrams (PI&D) and floor diagrams are illegible

Submission Problems - Data

- ❑ Where's the data? Missing sterilization, cleaning, environmental monitoring, process qualification, validation, extractable, leachable, container closure, media simulations, product lots, stability, and more (check CMC or CTD guidance)
- ❑ Changes for supplements are not implemented – unless you show how the change affects the product, it's a proposal 21 CFR 601.12(a)(2)
- ❑ No bridging studies for pilot to full scale or scale up

Submission Problem - Data

- ❑ Submission for a new area for fill and finish also included a change to the container closure that wasn't mentioned in the cover letter and the data to support the change was not submitted
- ❑ Change in multi-product contact equipment submission didn't have data from representative products. Data was later generated and one of the products failed stability, therefore change was not implemented for that product

Submission Problem - Data

- Supplement for a transfer of the same manufacturing process to a new location without considering the impact of the equipment and scale differences. Eventually the production cycles changed and led to multiple review cycles.
- A supplement was submitted for a new manufacturing area and a process scale up. The conformance lot data supporting the new manufacturing area included equipment no longer in use. Additionally, there was no supporting data for the process scale up at the time of submission.

Submission Problem - Data

- ❑ Submission for use of new bioreactors identical to ones already in use, but no data to support they operate the same way and no data to support the lack of adverse effect of the change on the identity, strength, quality, purity, or potency of the product
 - ❑ Submission included changes to a BSL-2 enhanced containment area with no data to support the change did not impact the HVAC or surrounding areas
 - ❑ Engineering lots manufactured but no data to support lots for introduction into interstate market
-

STEP 5

KNOW WHAT CAN BE AN
INSPECTION PROBLEM

Inspection Problems - Quality

- ❑ Qualification, validation not completed, not reviewed and signed off
- ❑ Deviations, non-conformances, over action limits, and out of specifications not documented, investigated, and completed
- ❑ Staff not following standard operating or other procedures

Inspection Problems - Quality

- ❑ Corrections made on batch records and documents without explanation
- ❑ Each step in the batch record is not documented
- ❑ Lack of quality unit review and sign off
- ❑ Batch records do not reflect the current process
- ❑ The process and data submitted with the BLA or supplement is not the same at the inspection site

Inspection Problems – Production and Process

- ❑ No rationale and or data to support implementation of changes
- ❑ Manufacturing process shows lack of control – bioburden, sterility, in-process, release test failures without addressing the problem and implementing corrective action

Inspection Problems

- ❑ Impact of new raw materials and components not completely evaluated and documented
- ❑ Lack of orderly storage of components, intermediate or bulk product
- ❑ Laboratory is not following CGMP

Inspection Problems Examples

- During an inspection it was discovered:
 - one of the facilities used in the manufacture of the product was not submitted – file had to be updated to include the location
 - transfer of the production step to a new contract facility did not include the following: – Process validation at the production scale on the line submitted in the supplement – No data for comparability for the addition of a secondary manufacturing line, of which they intended to use once the contract facility was approved

Inspection Problems Examples

- During an inspection it was discovered:
 - lots submitted as conformance lots were not manufactured using the equipment to be used for the full scale process
 - Mixing of final formulated bulk did not include a validated mixing time
 - Repeated excursions in the WFI system occurred without an investigation
 - The distributed control system (DCS) was not qualified to handle atypical manufacturing sequences during normal production

Product Quality

The diagram features a central green globe with five white arrows pointing towards it from below. A large green arrow curves around the globe, pointing from the right side towards the top-left. Below the globe, several white boxes with black text are arranged in a hierarchical structure, connected to the globe by thin white lines. The top box is 'Product Quality', followed by 'Quality System Directed by Quality Unit'. Below this are three boxes: 'Facilities & Equipment System', 'Production System', and 'Packaging & Labeling System'. Under 'Facilities & Equipment System' is 'Laboratory System'. Under 'Packaging & Labeling System' is 'Materials System'. At the bottom are three boxes: 'RECORDS', 'TRAINING', and 'PROCEDURES'. To the right of the globe, a white box contains the text 'CI, CAPA'.

Quality System Directed by Quality Unit

CI, CAPA

Facilities &
Equipment System

Production System

Packaging &
Labeling System

Laboratory System

Materials System

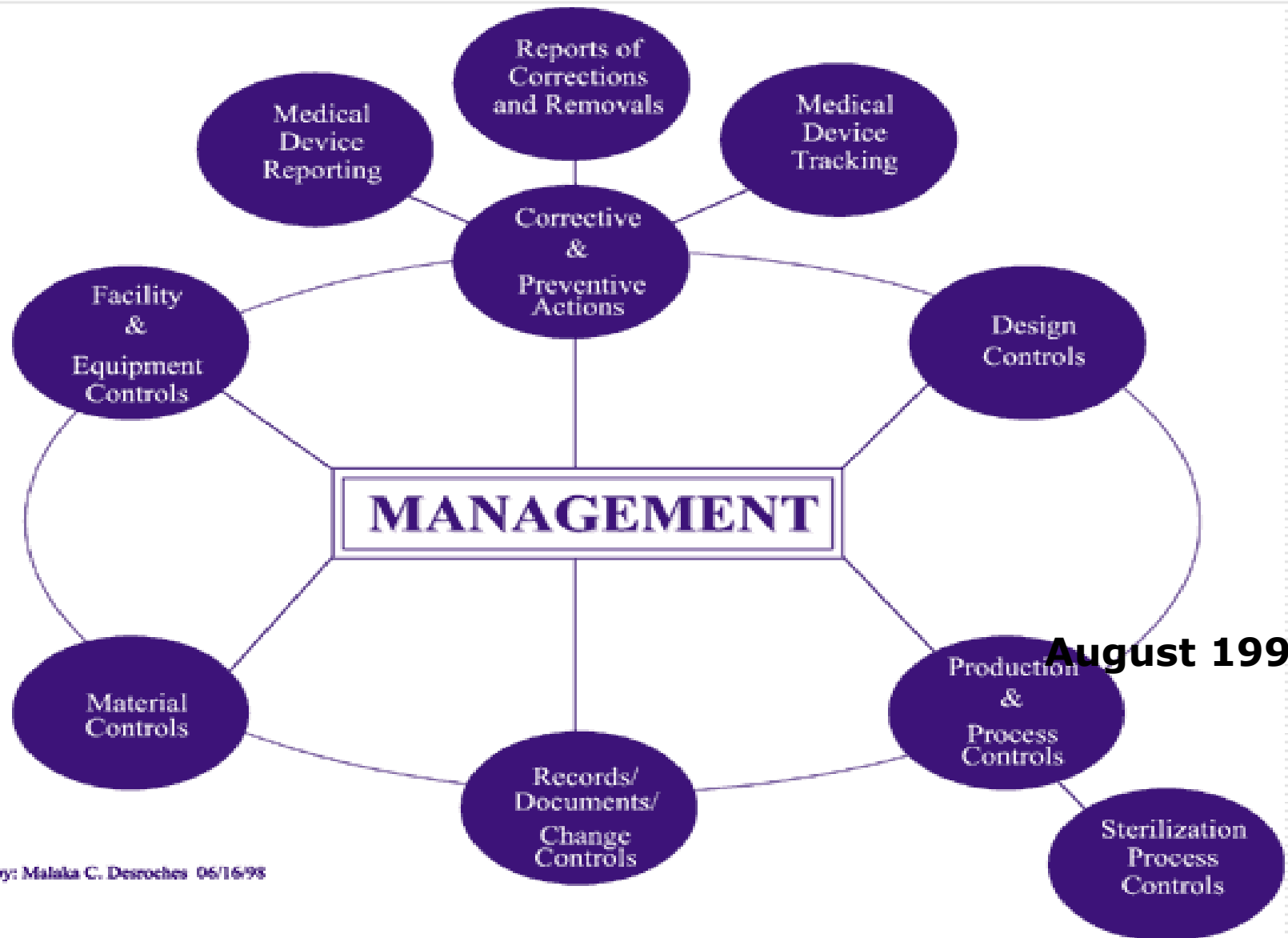
RECORDS

TRAINING

PROCEDURES

ORA / CDRH

Guide to Inspections of Quality Systems (Medical Devices)



Quality

- ❑ “A measure of a product’s or service’s ability to satisfy the customer’s stated or implied need.” – *Guidance for Industry Quality Systems Approach to Pharmaceutical CGMP Regulations* (Drugs – CDER, CBER, CVM, ORA)
- ❑ “Quality means the totality of features and characteristics that bear on the ability of a device to satisfy fitness-for-use, including safety and performance.” 21 CFR 820.3(s) (Devices)

Summary

- ❑ Open communication with FDA
- ❑ Follow statutes and regulations
- ❑ Strongly consider guidance
- ❑ Submission format and ease of use important for expedient review
- ❑ Don't bury important information – we'll find it in the end and may hold up approval

Summary

- ❑ Complete the BLA before submitting
- ❑ Submit the required data
- ❑ Complete qualification, validation
- ❑ Inquire if conformance lots, lot release lots, stability lots are needed
- ❑ Review and sign documentation



Thank You

- ❑ Mary Malarkey
- ❑ Jay Eltermann
- ❑ Laurie Norwood
- ❑ Chris Joneckis
- ❑ Michael Orr, Ron Wange CDER

- ❑ DMPQ co-workers – help & ideas for this talk
- ❑ FDA colleagues for their persistence and dedication