Combination Products: Lessons learned on Product Development and Regulatory Submissions

Navigating challenges to reduce time & risk

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REGULATORY COMPLIANCE ASSOCIATES® INC.

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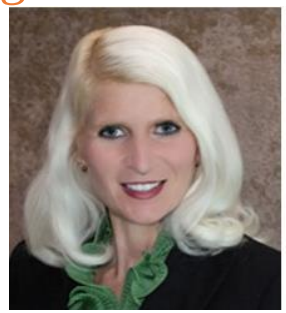


Learning Objectives

Combination Products

Reduce Time and Risk by:

1. Simplify the requirements and navigate complex regulations
2. Review the Eight Step Strategic Regulatory Planning for a Combination Product
3. Establish product development strategies: implement and execute development via requirements, V&V testing, and the Design History File (DHF)
4. Incorporate lessons learned from challenging case studies

Combination Products
Reducing Time and Risk

Roles of Product Development and Regulatory Affairs in Reducing Time and Risk for Combination Products:

- Product Development
  - Obviously → Make the right thing
    → Make it right
    → Support the product through it's entire lifecycle
  - But, also, maximize the effectiveness of Cross-functional activities

- Regulatory Affairs
  - Key hurdle in Combination Products is to establish and execute the Regulatory Strategy
  - How can Product Development support the Regulatory Strategy?

FDA Oversight of Combination Products

OFFICE OF COMBINATION PRODUCTS (OCP)

FDA's Office of Combination Products (OCP)

FDA's **Office of Combination Products (OCP)** is responsible for the following activities:

- Prompt assignment of a **Lead Agency Center** that will have primary jurisdiction for the review and regulation of a combination product
- Ensuring timely and effective premarket review by overseeing the timeliness of and coordinating reviews involving more than one Agency Center
- Ensuring consistent and appropriate post-market regulation of combination products
- Resolution of disputes regarding the timeliness of premarket review of combination products

FDA's Office of Combination Products (OCP) Continued

- OCP's assignment to an **Agency Center** is based on the Combination Product's **Primary Mode of Action (PMOA)** – the single mode of action of a combination product that provides the most important therapeutic action of the combination product.
- **Agency Centers** responsible for the pre-market review of the Combination Product may include:

– Center for Biologics Evaluation and Research (CBER)

– Center for Drug Evaluation and Research (CDER)

– Center for Devices and Radiological Health (CDRH)

Eight Step Strategic Regulatory Planning for a Combination Product

- **Step 1** – Define the Combination Product / Constituent Parts / Primary Mode of Action (PMOA)
- **Step 2** - Prepare a Preliminary Regulatory Strategy
- **Step 3** – Submit a Pre-Request for Designation (Pre-RFD)
- **Step 4** – Revise/Update the Regulatory Strategy based on FDA's Preliminary Informal, Non-Binding Designation
- **Step 5** – Submit a Request for Designation (RFD)
- **Step 6** – Revise/Update the Regulatory Strategy based on FDA's Formal, Binding Designation Letter
- **Step 7** – Early Collaboration Meeting with Lead Agency Center / Pre-Submission (PreSub) Meeting
- **Step 8** – Submit Marketing Application / Marketing Applications to Lead Agency Center

Step 1

DEFINE THE COMBINATION PRODUCT / CONSTITUENT PARTS / PRIMARY MODE OF ACTION (PMOA)

Combination Products Defined

Combination Products are defined in 21 CFR 3.2(e). The term Combination Product includes:

(1) A product comprised of two or more regulated components, (i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic), that are physically, chemically, or otherwise combined or mixed and produced as a single entity;

(2) Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products;

(3) A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, (e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose); or

(4) Any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect.

Combination Products - Device

Pursuant to Section 201(h) of the Food, Drug, and Cosmetic Act (21 U.S.C. 321(h)), a **device** is defined as follows:

Device – An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory which is:

1. Recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them,
2. Intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
3. Intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.

Combination Products - Drug

Pursuant to Section 201(g) of the Food, Drug, and Cosmetic Act (21 U.S.C. 321(g)), a **drug** is defined as follows:

Drug – An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory which is:

(A.) Articles recognized in the official United States Pharmacopeia, official Homeopathic Pharmacopeia of the United States, or official National Formulary, or any supplement to any of them; and

(B.) Articles intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals; or

(C.) Articles (other than food) intended to affect the structure or any function of the body of man or other animals; and

(D.) Articles intended for use as a component of any articles specified in Clause (A), (B), or (C).

Combination Products - Biologic

Pursuant to Section 351(i) (as modified by the Patient Protection and Affordable Care Act) of the Public Health Service Act (PHS Act) (42 U.S.C. 262(i)), a **biological product** is defined as follows:

Biological Product – A virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.

Combination Products – Constituent Parts

21 CFR 3.2(e) defines a **Combination Product** as one comprised of any combination of the following **Constituent Parts**:

- **Drug and Device**
- **Biological Product and Device**
- **Drug and Biological Product**
- **Drug, Device, and Biological Product**

Combination Products may be categorized as a Drug, Device, or Biologic based on its Primary Mode of Action (PMOA)

The following products do NOT meet the definition of a Combination Product as defined in 21 CFR 3.2(e):

- Drug - Drug
- Device - Device
- Biologic - Biologic

Primary Mode of Action (PMOA)

- **Primary Mode of Action (PMOA)** – the Single Mode of Action of a Combination Product that provides the most important Therapeutic Action of the Combination Product

Device	Drug	Biologic
Premarket Notification [510(k)] or Premarket Authorization [PMA] and Investigational Device Exemptions [IDE]	New Drug Application [NDA] and Investigational New Drug Application [IND]	Biologic License Application [BLA] and Investigational New Drug Application [IND]
CDRH	CDER	CBER

Step 2

PRELIMINARY REGULATORY STRATEGY

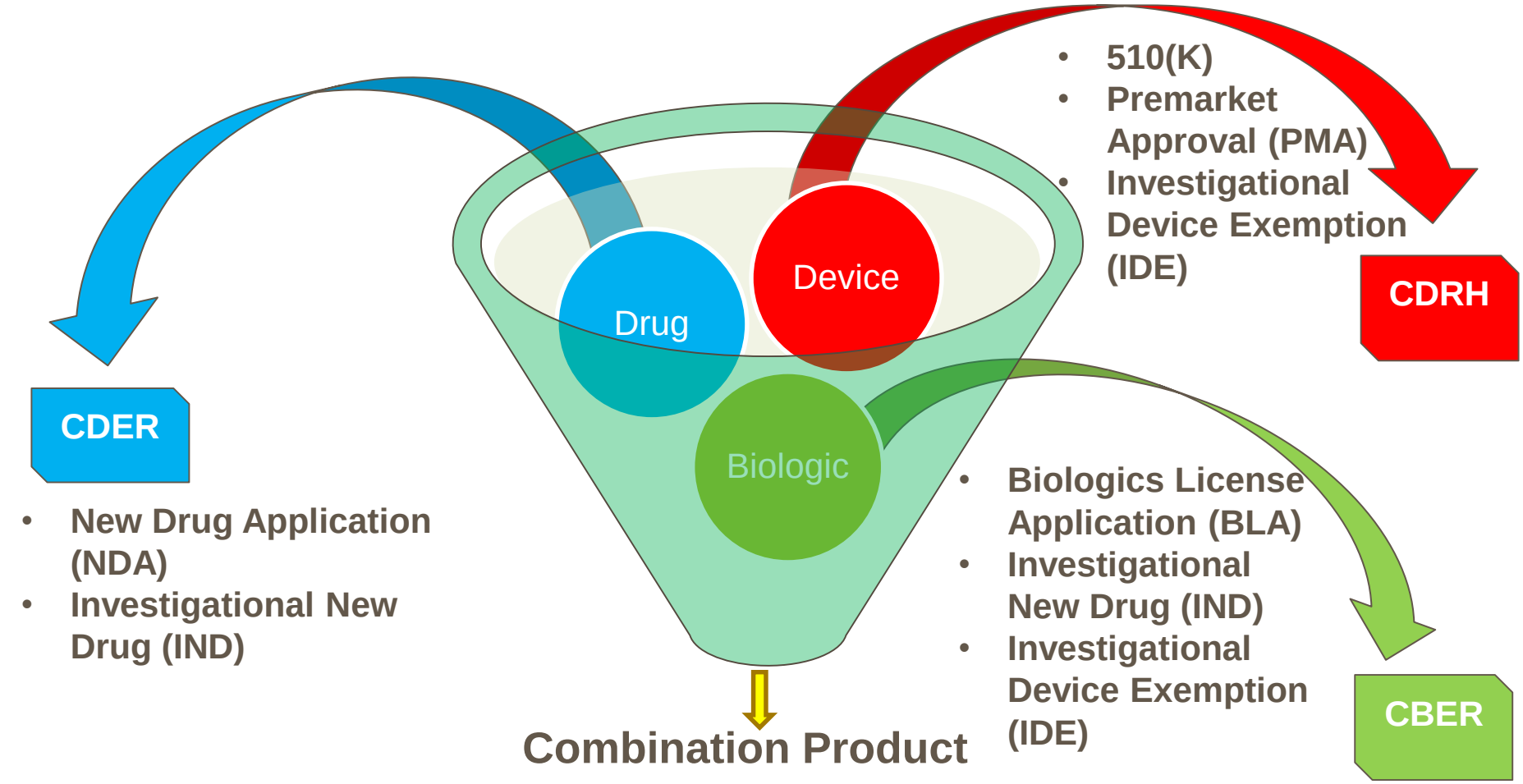
Preliminary Regulatory Strategy

The “Preliminary Regulatory Strategy” or ”Preliminary Regulatory Assessment” is the strategic regulatory planning document which outlines the submission requirements for the product, timeframes, and costs

WHEN? As early as possible [Phase 0/1; Concept Phase; etc.]

- It is a controlled document similar to a project plan
- It defines all regulatory requirements and product specifications, timing, resources, cost and strategic decisions
- It is used for a new product or modifications to a currently approved / cleared / licensed product
- Used for all FDA regulated product types (device, drug, biologic, combination product)

Preliminary Regulatory Strategy



Preliminary Regulatory Strategy

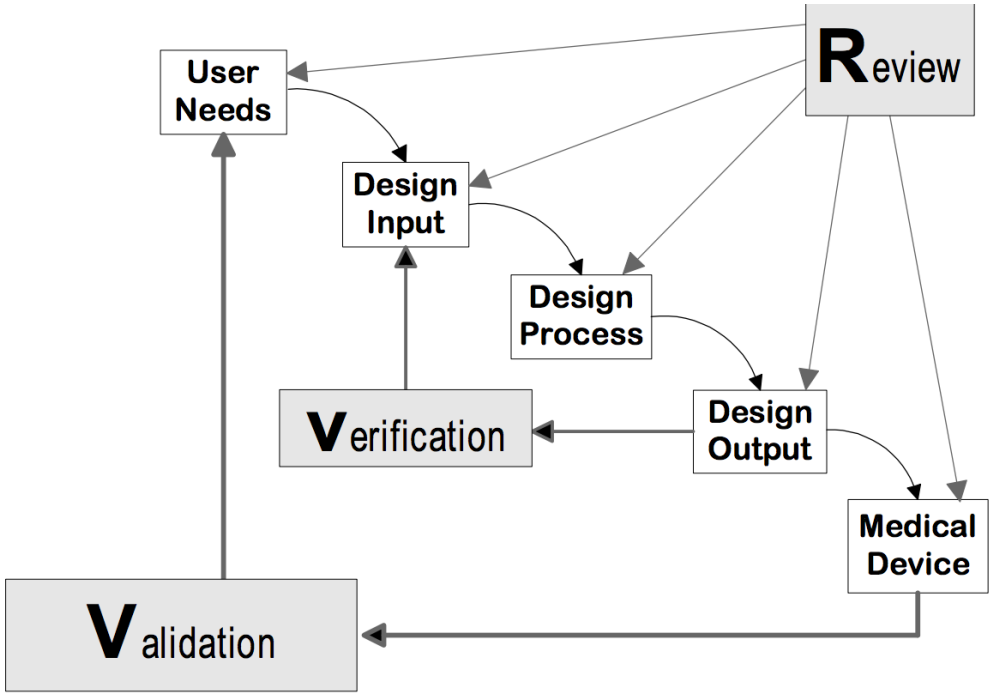
Critical Elements of the Preliminary Regulatory Strategy

- Detailed Description of the Combination Product / Constituent Parts – Prior cleared, approved or licensed parts (if applicable)
- Primary Modes of Action (PMOA)
- Product / Regulatory / Post-Market Safety Requirements for Combination Product/Constituent Part Applicants
- Proposed Intended Use / Indications for Use
- Proposed Product(s) Classification
- Proposed Risks – Benefits / Combination Product Specific Use Related Risk Analysis
- Proposed Claims & Labeling
- Proposed Pre-Clinical Testing / Bench & Performance Testing / Non-Clinical Testing / Clinical Testing / Clinical Studies Required / Leverage Existing Data
- Standard Operating Procedures (SOPs) / Systems / Standards / Guidance Documents
- Manufacturing and Compliance Requirements
- Possible Regulatory Submission Pathways and Requirements [510(K), PMA, NDA, BLA] including time & cost
- Planning of Pre-Request for Designation / Request for Designation / Early Communication and Pre-Submission Meetings with FDA
- Resources (Internal/External) / Costs / Budgets / Timelines
- Legal Considerations / Requirements for Co-Development and/or Existing Applications / Intellectual Property

Planning

- All Plans from the Design & Development Phase Require Outputs from Product Development for their completion
  - Regulatory Plans
  - Design Transfer Plans (Manufacturing)
  - Design Verification & Validation Plans with Traceability
  - Quality Plans
  - Risk Management Plans
- Anticipate Necessary Outputs to shorten and strengthen the product designs
- NOTE: All Plans are “living documents” and should be revisited or updated in each phase of product development.

Regulatory Strategy and Design Controls



Step 3

INFORMAL PRE-REQUEST FOR DESIGNATION (PRE-RFD)

Pre-Request for Designation (Pre-RFD)

- Pre-RFD process provides **informal, non-binding feedback** regarding the regulatory identity or classification of a human medical product as a **drug, device, biological product**, **or combination product**
- Provides information about a non-combination or combination product's assignment to the appropriate Agency Center who will have jurisdiction for the premarket review and regulation if it is a Combination Product:
  - Center for Drug Evaluation and Research (CDER)
  - Center for Devices and Radiological Health (CDRH)
  - Center for Biologics Evaluation and Research (CBER)

  Timing: Within (5) five business days of its receipt, the OCP will review the Pre-RFD to ensure it includes adequate information necessary for the preliminary assessment. OCP's goal to provide feedback on a Pre-RFD is 60 calendar days after complete information is received

Pre-Request for Designation (Pre-RFD) Continued

Pre-RFD Submission must include:

- Description of the Product
- Proposed Use or Indications for Use
- Description of how a product achieves its intended therapeutic/diagnostic effects
- No Page Limit for submission

Recommended, but Optional Information may include:

- Description of Manufacturing Processes including the sources of all components
- Supportive Data/Studies
- Analysis of Classification, Primary Mode of Action (PMOA) if it's a Combination Product, and Jurisdictional Assignment
- Description of Related Products
- Sponsor Recommendation

Step 4

REVISE/UPDATE PRELIMINARY REGULATORY STRATEGY

Considerations for the Revision / Update to the Preliminary Regulatory Strategy

- Confirm Methods for Demonstrating Safety and Effectiveness of a Combination Product and its Constituent Parts
- Resolution of Scientific / Technical Issues related to the Combination Product / Constituent Parts
- Use of Data/Information of Previously Approved, Cleared, or Licensed Constituent Part(s)
  - Indications for Use of Individual Constituent Part(s) versus the Combination Product
- Pre-Clinical and Non-Clinical Testing performed on Constituent Part(s) and required for the Combination Product
- Confirm Intended Use, Indications for Use, Target Population(s)
- Developmental Studies should be considered for the Constituent Parts alone AND for the finished Combination Product
- Number of Marketing Applications – Single or Multiple Applications

Regulatory Submission Types for Combination Products / Constituent Parts

Number of Marketing Applications – Single or Multiple Applications?

- 510(K) / PMA
- Biologics License Application (BLA)
- New Drug Application (NDA)

Investigational Application – Assessed for the entire Combination Product. Type of Investigational Application required for the Combination Product is defined by the Lead Agency Center assigned to perform the premarket review based on the designated PMOA

- Combination Product regulated as a Drug > Investigational New Drug Application (IND)
- Combination Product regulated as a Device > Investigational Device Exemption (IDE)
- Combination Product regulated as a Biologic > Investigational New Drug Application (IND)

Device	Drug	Biologic
Premarket Notification [510(k)] or Premarket Authorization [PMA] and Investigational Device Exemptions [IDE]	New Drug Application [NDA] and Investigational New Drug Application [IND]	Biologic License Application [BLA] and Investigational New Drug Application [IND]
CDRH	CDER	CBER

Step 5

FORMAL REQUEST FOR DESIGNATION (RFD)

Request for Designation - (RFD)

- RFD process provides **formal, binding determination** for the Sponsor's product with respect to the classification a drug, device, biological product, or combination product and/or Agency Center assignment

RFD Submission must include:

- Description of the Product
- Proposed Use or Indications for Use
- Description of Manufacturing Processes including the sources of all components
- Supportive Data/Studies
- Description of how a product achieves its intended therapeutic/diagnostic effects
- Analysis of Classification, Primary Mode of Action (PMOA) if it's a Combination Product, and Jurisdictional Assignment
- Description of Related Products
- Sponsor Recommendation
- Page Limit cannot exceed 15 pages

Step 6

FINALIZE REGULATORY STRATEGY

Considerations for the Final Regulatory Strategy

- Based on the formal, binding Request for Designation Determination
- Must address any Mitigations from Risk Management Procedures
- Must address any Product Modification / Design Changes / Changes to Manufacturing Processes
- Must address Unfavorable Preclinical/Clinical Test Results / Identify and Confirm additional testing required for the Combination Product
- Any other changes to the scope of the project
- Confirm whether a Single Marketing Application is sufficient or whether Multiple Marketing Applications are necessary for the Combination Product and its Constituent Parts
- Confirm Post Market Safety Requirements & Responsibilities of the Combination Product/Constituent Part Applicants
- Confirm Resources / Timelines / Milestones / Costs

Considerations for Final Regulatory Strategy – Single or Multiple Applications

Single Marketing Application	Multiple Marketing Applications
• Typically sufficient for clearance, approval, or licensure of the Combination Product • For Combination Products that are chemically, physically, or otherwise combined into one single entity • For most co-packaged Combination Products with Constituent Parts that could not be provided separately • For Combination Products for which separate applications would create regulatory inconsistency	• Multiple applications may be required by FDA when one of the Constituent Part(s) is already approved for another use; • When already approved product is subject to legal requirements different from those that will apply to the Combination Product • When Labeling of the already approved product will need to be changed to reflect its new intended use in the Combination Product

- A Combination Products for which a single marketing application is submitted should be subject to the fee associated with the type of application. Sponsors may be eligible for fee waivers or reductions
- When a Sponsor chooses to submit two applications covering the various components of a Combination Product when one application would suffice, two application fees would be assessed – one fee for each application. This is also true when FDA requires two applications for a combination product – two application fees would be assessed.

Step 7

EARLY COLLABORATION / PRE-SUBMISSION (PRE-SUB) MEETINGS

Early Collaboration / Pre-Submission (Pre-Sub) Meetings

- Early and frequent communication with the FDA about the Combination Product and the planned Marketing Application(s) is highly recommended to ensure a smooth regulatory pathway to product launch
- The Agency Centers (CDRH / CBER / CDER) provide extensive guidance on Early Collaboration and/or Milestone Meetings throughout the development process and prior to the submission of Investigational / Marketing Applications for the Combination Product
- Pre-Submission Meetings with FDA are critical opportunities to obtain valuable feedback from the Agency on their expectations related to the proposed testing and other supporting data/information required for the Marketing Application(s) of the Combination Product

Step 8

SUBMIT REQUIRED MARKETING APPLICATION(S)

Device Constituent Part of a Combination Product

DEVICE SUBMISSION(S)

Submission Requirements

- Cross-Labeled Products are independent products, and each constituent follows the appropriate regulatory requirements
- Co-Packaged or Single Entity Products must satisfy the regulatory requirements for both (all) constituents
- BUT, 21CFR 4.4(b) allows for the Streamlined Process
  - The intent of cGMP and QSR is the same and provides significant redundancies
  - To demonstrate full compliance with both regulations, a manufacturer that chooses to base its quality system on a cGMP-platform is required, as applicable, to additionally demonstrate compliance with specified provisions of the QSR, thus creating a *streamlined* (i.e., hybrid) quality system
  - Similarly, if starting with a QSR-platform, as applicable, include additional, necessary provisions of the cGMP requirements

Streamlined cGMP Approach

cGMP-based system (21CFR 210/211):

– Add the following provisions from the QS regulation in accordance with 21CFR 4.4(b)(1)

- 21CFR 820.20 Management responsibility
- 21CFR 820.30 Design controls
- 21CFR 820.50 Purchasing controls
- 21CFR 820.100 Corrective and preventive action
- 21CFR 820.170 Installation
- 21CFR 820.200 Servicing

Streamlined QSR Approach

QSR-based system (21CFR 820):

- Add the following provisions from the drug cGMPs in accordance with 21CFR 4.4(b)(2)
  - 21CFR 211.84 Testing and approval or rejection of components, drug product containers, and closures
  - 21CFR 211.103 Calculation of yield
  - 21CFR 211.132 Tamper-evident packaging requirements for over-the-counter (OTC) human drug products
  - 21CFR 211.137 Expiration dating
  - 21CFR 211.165 Testing and release for distribution
  - 21CFR 211.166 Stability testing
  - 21CFR 211.167 Special testing requirements
  - 21CFR 211.170 Reserve samples

510(K) Requirements

- Medical Device User Fee Cover Sheet (Form FDA 3601)
- CDRH Premarket Review Submission Cover Sheet
- 510(k) Cover Letter
- Indications for Use Statement
- 510(k) Summary or 510(k) Statement
- Truthful and Accuracy Statement
- Class III Summary and Certification
- Financial Certification or Disclosure Statement
- Declarations of Conformity and Summary Reports
- Executive Summary
- Device Description
- Substantial Equivalence Discussion
- Proposed Labeling
- Sterilization and Shelf Life
- Biocompatibility
- Software
- Electromagnetic Compatibility and Electrical Safety
- Performance Testing – Bench
- Performance Testing – Animal
- Performance Testing – Clinical
- Other

Premarket Approval (PMA) Requirements

- Applicant Name and Address
- Table of Contents
- Summary Section
- Indications for Use
- Device Description
- Alternative Practices and Procedures
- Marketing History
- Summary of Studies
- Conclusions drawn from the Studies
- Complete Description of:
  - the device, including pictorial representations;
  - each of the functional components or ingredients of the device if the device consists of more than one physical component or ingredient;
  - the properties of the device relevant to the diagnosis, treatment, prevention, cure, or mitigation of a disease or condition;
  - the principles of operation of the device; and
- Methods, facilities, and controls used in the manufacture, processing, packing, storage, and where appropriate, installation of the device.
- Performance Standard or Voluntary Standard
- Technical Sections containing Data and Information including:
  - Results of Nonclinical Laboratory Studies
  - Results of Clinical Investigations involving Human Subjects
- A Bibliography of all published reports that concern the safety or effectiveness of the device.
- One or more samples of the device and its components, if requested by FDA.
- Proposed Labeling for the device.
- Environmental Assessment (EA) or Environmental Impact Statements (EIS)
- A Financial Certification or Disclosure Statement or both as required by 21 CFR 54.
- Such other information as FDA may request.
- Other Information (reference to Master File)
- Omissions
- Updates
- Color Additive

Drug Constituent Part of a Combination Product

DRUG SUBMISSION

New Drug Application (NDA) Requirements

- Application Form
- Index
- Summary
- Technical Sections
  - Chemistry, Manufacturing, and Controls Section
  - Nonclinical Pharmacology and Toxicology Section
  - Human Pharmacokinetics and Bioavailability Section
  - Microbiology Section
  - Clinical Data Section
  - Statistical Section
  - Pediatric Use Section
- Samples and Labeling
- Case Report Forms and Tabulations
- Other
- Patent Information
- Patent Certification
- Claimed Exclusivity
- Financial Certification or Disclosure Statement

Biologic Product Constituent Part of a Combination Product

BIOLOGIC PRODUCT SUBMISSION

Biologics License Application (BLA) Requirements

- Table of Contents (Index)
- Labeling
- Summary
- Chemistry, Manufacturing and Controls (CMC)
- Nonclinical Pharmacology and Toxicology
- Human Pharmacology and Bioavailability/Bioequivalence
- Clinical Microbiology
- Clinical
- Safety Update
- Statistical
- Case Report Tabulations (CRTs)
- Case Report Forms
- Patent Information
- Patent Certification
- Establishment Description
- Debarment Certification
- User Fee Cover Sheet
- Other

Lessons Learned

- The successful launch of a Combination Product is predicated on strategic, proactive, and long-term planning that begins in the early phases of Design & Development and lasts throughout the product lifecycle

- A comprehensive Regulatory Strategy must be created for the Combination Product in order to effectively prepare the Marketing Application(s) to ensure a smooth regulatory pathway for your Combination Product

- The Regulatory Strategy must be reviewed and updated at regular intervals in coordination with the overall project plan to identify and account for any changes to the scope of the project

- Early communication / collaborative meetings with FDA are critical for the successful launch of the Combination Product

Lessons Learned - continued

- Designing / Developing / Launching a Combination Product requires a disciplined and thoughtful approach to address the key factors that may impact the success of the project:
  - Manufacturing
  - Required Pre-Clinical / Non-Clinical / Performance / Functional / Clinical Studies, etc.
  - Post-Market Safety Requirements
  - Legal and Regulatory Requirements
  - Costs, Resources, Timelines

- For Improved efficiency during Development, “Think Backwards”
  - Product Claims should be represented by Product Requirements
  - Anticipate Verification and Validation plans and execution before writing Product Requirements

Questions?

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