Current GMP Requirements for Combination Products

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Definition of A Combination Product

- A product composed of two or more different types of medical products (i.e., a combination of a drug, device, and/or biological product with one another) (21 CFR part 3).
- Under 21 CFR 3.2(e), a combination product includes:
  - Single entity: 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.
  - Co-packaged: 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.
  - Cross-labeled: 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.
  - 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.

CGMP requirements for Combination Products

- 21 CFR § 4.3:
  - The current good manufacturing practice requirements in parts 210 and 211 of this chapter apply to a combination product that includes a drug constituent part;
  - The current good manufacturing practice requirements in part 820 of this chapter apply to a combination product that includes a device constituent part;
  - The current good manufacturing practice requirements among the requirements (including standards) for biological products in parts 600 through 680 of this chapter apply to a combination product that includes a biological product constituent part to which those requirements would apply if that constituent part were not part of a combination product; and
  - The current good tissue practice requirements including donor eligibility requirements for HCT/Ps in part 1271 of this chapter apply to a combination product that includes an HCT/P.
- Subpart B—Postmarketing Safety Reporting for Combination Products
  - Combination product applicants and/or constituent part applicants
  - All provisions of 21 CFR Part 4, Subpart B are enforceable

CGMP Requirements for Single-entity and Co-packaged Combination Products

- Option 1:
  - Manufacturers demonstrate compliance with all CGMP regulations applicable to each of the constituent parts included in the combination product (21 CFR 4.4(a))
- Option 2: A CGMP Operating System
  - A drug CGMP-based streamlined approach
    - The drug CGMPs with "Called-out" provisions from the device QS regulation (21 CFR 4.4(b)(1))
  - A device QS regulation-based streamlined approach
    - The device QS regulation "Called-out" provisions from the drug CGMPs (21 CFR 4.4(b)(2))
- For a combination product that includes a biological product, the manufacturer must demonstrate compliance with the CGMP requirements specific to biological products in 21 CFR parts 600 through 680.
- For a combination product that includes any HCT/P, the manufacturer must demonstrate compliance with the regulations in 21 CFR part 1271—including the current good tissue practice (CGTP) requirements and donor eligibility requirements.

CGMP Requirements for Cross-labeled Combination Products

- At separate facilities:
  - constituent parts need only comply with the requirements otherwise applicable to that type of product
- At the same facility:
  - A streamlined CGMP operating system for the manufacture of the combination product
  - Distinct systems for the manufacture of each constituent part

- In the event of a conflict between regulations applicable under the regulations to combination products, the regulations most specifically applicable to the constituent part in question shall supersede the more general.

Compliance Programs for Product Inspections

- Compliance Program 7346.832: For pre-approval inspections of CDER-led combination products approved under an Abbreviated New Drug Application (ANDA) or a New Drug Application (NDA).
- Compliance Program 7356.000: Inspections of CDER-led or CDRH-led Combination Products
- Compliance Program 7356.002M: For pre-licensing and surveillance inspections of CDER-led combination products approved under a Biologics License Application (BLA).
- Compliance Program 7383.001: For pre-approval inspections of CDRH-led combination products (Premarket Approval (PMA)).
- Compliance Program 7356.002: For surveillance inspections of CDER-led NDA/ANDA combination products.
- Compliance Program 7382.845: For surveillance inspections of CDRH-led combination products.
- Compliance Program 7345.848: For Pre-license/Pre-approval, and Post-Market Inspections of CBER regulated Biological Drug Products
- Compliance Program 7341.002: For surveillance Inspections of CBER regulated o human cells, tissues, and cellular and tissue-based products (HCT/Ps)

Compliance Programs for Combination Product Inspections

Compliance Program 7356.000: Inspections of CDER-led or CDRH-led Combination Products

- This Compliance Program focuses on two types of combination products:
  - Single-entity combination product: The constituent parts are physically or chemically combined (e.g., a prefilled syringe or drug-eluting stent). See 21 CFR 3.2(e)(1).
  - Co-packaged combination product: The constituent parts are packaged together (e.g., a surgical or first-aid kit containing devices and drugs, a delivery device packaged with a container of drug product). See 21 CFR 3.2(e)(2).
  - Manufacturers of constituent parts of cross-labeled combination products need only comply with the requirements otherwise applicable to that type of product (or apply a streamlined CGMP operating system).
- This combination product compliance program should NOT be used for:
  - Facilities that manufacture only one type of constituent part of a combination product (e.g., only the drug, device, or biological product).
  - Facilities that manufacture only “components” (e.g. device components, or APIs)
- For pre-approval, post-approval, surveillance, for cause, and other risk-based inspections.
- The lead center serves as the primary point of contact related to an inspection of a combination product

Approach for Combination Product CGMP Inspections

- Determine the CGMP operating system chosen by the combination product manufacturer
  - Option 1 vs. Option 2
- Determine the facility's manufacturing and CGMP responsibilities
  - CGMP activities for a combination product may occur at multiple facilities
  - Inspectional coverage should be of those CGMP activities occurring at the facility.
- Conduct an inspection under the commodity-specific compliance program relevant to the base CGMPs and type of inspection
  - Use of inspectional elements from the base program for each constituent part and the combination product
  - Coverage of the relevant called-out provisions of 21 CFR Part 4
- Generally, combination product manufacturers use a streamlined approach with base CGMPs that align with the application type

Scope of Combination Product Inspections

- The Lead Center should provide the scope of inspection coverage of manufacturing activities at the facility
- Inspectional coverage should be of those CGMP activities occurring at the facility
  - A facility that manages only the design activities for the combination product,
  - A facility that only sterilizes a combination product
- The focus of the inspection should be on the combination product for which marketing approval is sought

General Approach to Pre-Approval Inspection Coverage for Combination Product Facilities

Application Type for Pre-Approval Inspection	Base CGMPs	Base Compliance Program	Additional Coverage of Called-out Provisions
NDA/BLA/ANDA	Drug CGMP (21 CFR Part 211)	7346.832 (NDA/ANDA) 7356.002M and 7356.002A (BLA)	Management Controls (21 CFR 820.20) Design Controls (21 CFR 820.30) Purchasing Controls (21 CFR 820.50) CAPA (21 CFR 820.100) Installation (21 CFR 820.170) and/or Servicing (21 CFR 820.200), if appropriate
PMA	Device QS (21 CFR Part 820)	7383.001	Testing and approval or rejection of components, drug product containers, and closures (21 CFR 211.84) Calculation of yield (21 CFR 211.103) Tamper-evident packaging requirements for over-the-counter (OTC) human drug products (21 CFR 211.132) Expiration dating (21 CFR 211.137) Testing and release for distribution (21 CFR 211.165) Stability testing (21 CFR 211.166) Special testing requirements (21 CFR 211.167) Reserve samples (21 CFR 211.170)

Profile Codes for Combination Product Manufacturers

- FDA ORA Investigations Operations Manual (IOM) 2022, Chapter 5: Establishment Inspections
  - 5-14.7 Profile Classes and Codes
    - Table 5-14.7.1.1 Biologics
    - Table 5-14.7.1.2 Devices
    - Table 5-14.7.1.3 Drugs and Veterinary

- CDER-led combination product manufacturers should have at least one drug profile code and one device profile code
  - For a sterile-filled prefilled syringe manufacturer, use profile codes SVS: Sterile-filled small volume parenteral drugs and IDD: injectable delivery device (syringes, auto injectors/pens)).

Annotation of the FDA 483 for device inspections.

- IOM 5.2.3.4 - Annotation of the FDA 483 and FDA 4056
- Offer to annotate the FDA 483 for all medical device inspections
  - BIMO inspections are generally excluded from annotations.
- Inform the establishment of the annotation program at closeout prior to the final discussion with management.
- Determine from management whether they wish to have their FDA 483 observations annotated.
- The actual annotation of the FDA 483 should occur during the final discussion with management.
- The annotations can be made after each observation, at the end of each page of the FDA 483 or at the bottom of the last page of the FDA 483 prior to the investigator's signature.

Annotation of the FDA 483 for device inspections.

- If the establishment has promised and/or completed a corrective action to an FDA 483 observation prior to the completion of the inspection, the FDA 483 should be annotated with one or more of the following comments, as appropriate:
  - Reported corrected, not verified.
  - Corrected and verified.
  - Promised to correct.
  - Under consideration.
- When an establishment has promised corrections and furnishes a date or timeframe (without a specific date) for completion, then add "by xxx date" or "within xxxx days or months" in the annotation.

Annotation of the FDA 483 for device inspections.

- Handling disagreement
  - Where the investigator and the establishment have "agreed to disagree" about the validity of an observation on the FDA 483, the investigator may annotate this observation with "Under consideration" or with no annotation based on the establishment's desire.
  - The establishment's stated objections to any given observation or to the FDA 483, as a whole should not be annotated on the FDA 483.
  - If firm does not wish to annotate an FDA 483, it should be documented in the report
  - The EIR should include the establishment's objections to the observation and the fact the establishment declined to have the observation annotated.

Considerations for Combination Product CGMP Inspections

- User Fee Dates
  - PDUFA VII/BsUFA III
    - Original application submissions within 10 months of the 60 day filing date
  - GDUFA III
    - standard original ANDAs within 10 months of the date of ANDA submission
  - MDUFA V:
    - Original PMAs within 180-day of the date of filing with Substantive Interaction within 90 days and a total time to decision of 290 days.

Pre-approval Inspections for Combination Products

- For CDER-led NDAs/ANDAs/BLAs
  - CDER CMC review team issues an inter-center consult request to CDRH on the device component
  - CDER/ORA conducts PLI/PAI for drug establishment(s) referenced in the application if necessary
  - CDRH issues inspection recommendation to CDER CMC team for the device facility if necessary
  - CDER issues PAI request to ORA for device coverage
  - PAI EIR is sent to CDER from ORA once the PAI is completed
  - CDER requests a CDRH consult on EIR review and final inspection classification
  - CDER CMC makes the final recommendation on the application
- For CDRH-led PMAs
  - CDRH review team issues an inter-center consult request to CDER CMC on the drug component
  - CDER CMC team assesses the facilities referenced in the application to determine if a PLI/PAI is required
  - CDER or ORA (requested by CDER) conducts a PLI/PAI at facility for drug coverage
  - CDER or ORA issues the initial inspection recommendation to CDER CMC team for the drug facility
  - CDER conducts an EIR review and makes final inspection classification
  - CDER CMC makes the overall recommendation on the drug component to CDRH
  - CDRH makes the final recommendation on the application

Impact of CGMP Inspections on Combination Products

- Inspection decisions on CDER-led NDAs/ANDAs/BLAs
  - Establishment inspection is part of CMC assessment
  - For biological products, each establishment must complies with the standards established in the application and the requirements in regulations
  - Approval Letter
    - Inspection classification is acceptable
  - Completer Response Letter with Post Action Letter for CGMP deficiencies
    - Inspection classification is withhold or facility is under an OAI
- Inspection decisions on CDRH-led PMAs
  - Approval Letter
    - Inspection classification is acceptable
  - Not Approvable Letter
    - Inspection classification is withhold
  - Approvable Pending GMP Inspection Letter
    - FDA has not confirmed that manufacturing facilities, methods and controls are in compliance with Quality System

Combination Products with a Biological Product

For a combination product that includes a biological product, the manufacturer must demonstrate compliance with the CGMP requirements specific to biological products in 21 CFR parts 600 through 680.

Biologics Licenses: Issuance and Conditions

- 21 CFR 601.20: Biologics Licenses: Issuance and Conditions
  - Examination. A biologics license application shall be approved only upon examination …. and determination that the product complies with the standards established in the application and the CGMP requirements.
  - Inspection. A biologics license shall be issued ….. only after inspection … and upon a determination that the establishment(s) listed in application complies with the standards established in the application and the requirements in regulations.
  - Availability of product. No biologics license shall be issued unless:
    - (1) The product intended for introduction into interstate commerce is available for examination, and
    - (2) Such product is available for inspection during all phases of manufacture.
  - Manufacturing process. No product shall be licensed if any part of the process of or relating to the manufacture of such product, …… would impair the assurances of continued safety, purity, and potency as provided by the regulations.

Inspections for Biological Products

- 21 CFR 600.20 Inspectors.
  - Inspections shall be made by an officer of the FDA having special knowledge of the methods used in the manufacture and control of products.
- 21 CFR 600.21 Time of inspection.
  - The establishment is in operation and is manufacturing the complete product for which a biologics license is desired.
- 21 CFR 601.20 Biologics licenses; issuance and conditions.
  - Availability of product. No biologics license shall be issued unless:
    - The product intended for introduction into interstate commerce is available for examination, and
    - Such product is available for inspection during all phases of manufacture.
  - Inspection: establishment(s) complies with the standards established in the application and the requirements prescribed in applicable regulations.

Requirements for Biological License Applications

- Complete commercial scale process performance qualification (PPQ) studies (Stage 2b) and submit PPQ summary data in an application (2011 FDA PV Guidance)
- Type II Drug Master Files (DMFs) for a drug substance, drug substance intermediate, or drug product would not be acceptable for a BLA
  - The risk associated with the manufacture of complex biological products is generally significantly higher than that associated with the manufacture of chemical entities
  - The applicant for a BLA is expected to have knowledge of and direct control over the manufacturing process for the DS/DSI/DP of a biological product
- Facility is ready for inspection and is manufacturing the complete product for which a license is desired.
- Submit proposed manufacturing schedules for each DS, DSI, and DP manufacturing facility in the application.

Combination Product Inspection Case Study 1

- Application Type: A CDRH-led PMA combination product containing a biological product
- MDUFA timeline: 180-day
- Deficiency: The manufacturing site for the biological product has no scheduled production run within the application review period.
- Interactions between the FDA and the applicant:
  - An inspection must be conducted at the manufacturing site before the application can be approved.
  - The submission was placed on hold after issuing a deficiency letter (Substantive Interaction), which allowed the facility to schedule a production run.
  - A Pre-approval inspection was conducted during the review hold
  - A response to the deficiency letter was submitted to the Agency after all CGMP deficiencies were resolved.
- Final decision: Application was approved.

Combination Product Inspection Case Study 2

- Application Type: A CDRH-led PMA combination product containing a biological product
- MDUFA timeline: 180-day
- Deficiency: A pre-approval inspection must be conducted at the manufacturing site for the biological product to verify the adequacy of the proposed manufacturing process based on previous observations.
- Impact on application recommendation:
  - No other deficiencies were identified.
  - Option 1:
    - Approvable Pending GMP Inspection Letter per PMA
  - Option 2:
    - No decision until an inspection is conducted at the facility
  - Final recommendation:
    - An inspection must be conducted before the application can be approved.