Regulatory Expectations for Drug-Device Combination Products
CGMP Requirements

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What is a Combination Product?

Combination of 2 or more types of medical products:

- Drug + Device
- Device + Biologic
- Drug + Biologic
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Types of Combination Products

- Three kinds defined in 21 CFR 3.2(e):
  - “Single-entity” (e.g., drug-eluting stent)
  - “Co-package” (e.g., first-aid or surgical kit, or a syringe packaged with vial of a drug)
  - “Cross-labeled” (e.g., certain light-emitting devices and light-activated drugs)

- Biological products also meet the definition of a drug or device, and human cellular and tissue-based products (HCT/Ps) may be constituent parts of combination products and regulated as drugs, devices, or biological products.

- Note that drug-drug combinations are “fixed dose combination products,” not combination products under 21 CFR Part 3
Deciding Review Jurisdiction

- Combination products are assigned to a Center based on Primary Mode of Action (PMOA) – FDCA 503(g) and 21 CFR 3.2(m)
  - Drug PMOA = CDER
  - Device PMOA = CDRH
  - Biologic PMOA = CDER (e.g., therapeutic protein) or CBER (e.g., vaccine)

- Examples of CDER-led combination products
  - Pre-filled syringes
  - Pre-filled autoinjectors
  - Photodynamic therapy
  - Iontophoretic drug delivery patch and controller
  - Transdermal patches
  - Antibody-drug conjugates
21 CFR Part 4
CGMPs for Combination Products
CGMP Rule for Combination Products (21 CFR part 4)

- Existing CGMP regulations established minimum requirements to assure the safety, identity, strength, quality and purity, as applicable, of drugs, devices, biological products, and HCT/Ps.

- Combination products rule (final rule issued on January 22, 2013) addresses how to satisfy these CGMP requirements to ensure manufacture of a safe and effective product while avoiding redundant regulatory obligations.
CGMP Rule for Combination Products

• *Streamlined approach*. Co-packaged and single-entity combination products manufacturers that are subject to both the drug CGMPs and device QS regulation may:
  
  – Implement either the drug CGMPs (at 21 CFR 210 and 211) or device quality system regulation (at 21 CFR 820) rather than both,
  
  – IF they also implement specified provisions of the other of these two sets of CGMP requirements.

• The CGMPs for biological products under parts 600 through 680 and for HCT/Ps under part 1271 also must be met if applicable.
Specified Requirements from QS Regulation

- 21 CFR 820.20 - Management responsibility
- 21 CFR 820.30 - Design controls
- 21 CFR 820.50 - Purchasing controls
- 21 CFR 820.100 - Corrective and preventive action
- 21 CFR 820.170 – Installation (as applicable)
- 21 CFR 820.200 – Servicing (as applicable)
Specified Requirements from Drug CGMPs

- 21 CFR 211.84 - Testing and approval or rejection of components, drug product containers, and closures.
- 21 CFR 211.103 - Calculation of yield
- 21 CFR 211.132 - Tamper-evident packaging for over-the-counter (OTC) human drug products
- 21 CFR 211.137 - Expiration dating
- 21 CFR 211.165 - Testing and release for distribution
- 21 CFR 211.166 - Stability testing
- 21 CFR 211.167 - Special testing requirements
- 21 CFR 211.170 - Reserve samples
Final Guidance

Current Good Manufacturing Practice Requirements for Combination Products, January 2017

• Selection of CGMP operating system:
  – Combination product manufacturers can choose whichever they prefer among:
    • 211-based streamlined approach
    • 820-streamlined approach, or
    • non-streamlined approach (comply with both sets of regulations)
  – PMOA does not determine or dictate choice
Final Guidance

• Applicability of requirements:
  – Arise from constituent parts (e.g., if device constituent part would not be subject to 820 requirements, they do not apply to the combination product)
  – Facility that manufactures only a constituent part need only comply with the regulation for that constituent part (e.g., facility that only makes the device constituent part must only comply with 21 CFR 820)
  – Some requirements concern the product as a whole (e.g., design controls – 21 CFR 820.30)
  – Some requirements include considerations for the manufacturing process as a whole (e.g., data that may inform the CAPA system for the combination product)
Design Controls (21 CFR 820.30)

Design inputs and outputs
Risk analysis
Design history file

Design verification and validation
Design changes

• Confirm that there are no negative interactions between constituent parts, and ensure that their combined use results in a combination product that is safe and effective and performs as expected

• Apply to activities during product development as well as to postmarket changes to the design or manufacturing process

• Extent and complexity of the design controls process and associated documentation will vary based on the product
  – For example, consider a drug product already legally marketed with the same formulation, route of administration and intended use when marketed as part of a combination product that also incorporates a delivery device. Design controls would begin when the delivery device configuration is judged to be feasible and appropriate to develop.
# Design Controls vs. Pharmaceutical Development

<table>
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<tr>
<th>Design Controls Requirement</th>
<th>Pharmaceutical Development (ICH Q8(R2))</th>
<th>Comments</th>
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<tr>
<td><strong>Design Inputs</strong> (21 CFR 820.30(c))</td>
<td>Quality Target Product Profile</td>
<td>Develop design requirements that form the basis of product development and are appropriate to address the intended use of the product.</td>
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<tr>
<td><strong>Design Outputs</strong> (21 CFR 820.30(d))</td>
<td>Critical Quality Attributes</td>
<td>Capture product/process properties that must be controlled to ensure product quality.</td>
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<tr>
<td><strong>Design Verification</strong> (21 CFR 820.30(f))</td>
<td>Risk Assessment/Design Space</td>
<td>Identify potential product/material/process/user hazards and mitigate to ensure the safety and efficacy of the combination product for the user.</td>
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<td><strong>Design Validation</strong> (21 CFR 820.30(g))</td>
<td>Development of Control Strategy</td>
<td>Collect evidence to support that material controls and manufacturing process controls will ensure manufactured product meets required specifications/attributes.</td>
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<tr>
<td><strong>Design Transfer</strong> (21 CFR 820.30(h))</td>
<td>Development of Control Strategy</td>
<td>Establish controls over incoming materials and manufacturing process that ensure specifications or other attributes of the product design are maintained in the manufacturing environment.</td>
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Design Controls

• Apply to the whole combination product, not just the device constituent part

• For example, consider a drug in an automated injector. Design controls:
  – Apply to the automated injector (why was the injector designed this way – design inputs might include need for metered delivery of liquids, material selection for strength and biocompatibility)
    AND
  – Apply to the combination product (why was this injector selected as appropriate for this drug product – design inputs might include force to activate for intended patient population, ability to dispense drug of a certain viscosity)

• May also be appropriate to apply design controls to drug constituent part, for example, if newly formulated specifically for the combination
Facility Assessment for Combination Product ANDAs

• Combination products with a drug PMOA will generally have a facility assessment by both CDER/OPQ/OPF and CDRH’s Office of Compliance to ensure compliance with 21 CFR part 4, including:
  – Compliance with the 820 provisions
  – Whether a facility inspection is needed for facilities involved in the manufacture of the device constituent or the combination product (inspection typically performed by ORA, potentially with Center experts)

• This assessment is unrelated to whether or not there is a CDRH review of other aspects of the product (e.g., design, engineering, electrical safety)
820 Information in an ANDA*

For applicants using the streamlined approach of 211 + provisions of 820:

- **Management responsibility (21 CFR 820.20)**
  - Summary of how management has established responsibility to assure the combination product is manufactured in compliance with all applicable CGMP requirements.
  - Description of the functions and responsibilities of each facility involved in the manufacturing of the combination product and its constituent parts.

- **Design Control, General (21 CFR 820.30)**
  - Explain how you utilized the design control process to develop the combination product and provide a description of your design control procedures.
  - Address how requirements for design and development planning, design input, design output, design review, design verification, design validation, design transfer, design changes, and design history file are being met. Provide a copy or summary of the plan used to design the combination product.

- See FDA guidance *Quality System Information for Certain Premarket Application Reviews* (2003) for more information
820 Information in an ANDA

- **Purchasing Controls (21 CFR 820.50)**
  - Provide a summary of the procedure(s) for purchasing controls. The summary should:
    - Describe your supplier evaluation process and describe how it will determine the type and extent of control you exercise over suppliers.
    - Explain how you maintain records of acceptable suppliers and how you address the purchasing data approval process.
    - Explain how you will balance purchasing assessment and receiving acceptance to ensure that products and services are acceptable for their intended use.
  - Explain how the procedure(s) will ensure that changes made by contractors/suppliers will not affect the final combination product. Provide a description of how you apply the purchasing controls to the suppliers/contractors used in the manufacturing of the combination product. (e.g., through supplier agreements).
820 Information in an ANDA

• **Corrective and Preventive Action (21 CFR 820.100)**
  – Summarize the procedure(s) for your corrective and preventive action (CAPA) system. The CAPA system should require:
    • Identification of sources of quality data and analysis of these data to identify existing and potential causes of nonconforming practices and products;
    • Investigation of nonconformities and their causes;
    • Identification and implementation of actions needed to correct and prevent recurrence of nonconformities; and
    • Verification or validation of the actions taken.

• **Installation (21 CFR 820.170) and Servicing (21 CFR 820.200)** – only if applicable for device constituent part
Resources

• Final CGMP rule and guidance available on Office of Combination Products webpage
  (https://www.fda.gov/CombinationProducts/default.htm)

• Contact:
  – Office of Combination Products – for general combination product information
    • combination@fda.gov
  – CDER/OPQ for ANDA-related CGMP questions:
    • CDER-OPQ-Inquiries@fda.gov
THANK YOU