

CGMP Compliance Considerations for Combination Product Manufacturing

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Office of Manufacturing Quality



Office of Compliance mission:

Promote and protect the public health through strategies and actions that minimize consumer exposure to unsafe, ineffective, and poor quality drugs.



Office of Manufacturing Quality (OMQ):

We focus on the drug manufacturing aspect of CDER/OC's mission

Combination Products

Under 21 CFR 3.2 (e):

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.

(“Single-entity combination product”).

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. (“Co-packaged combination product”)

Combination products

a drug and a device

a biological product and a device

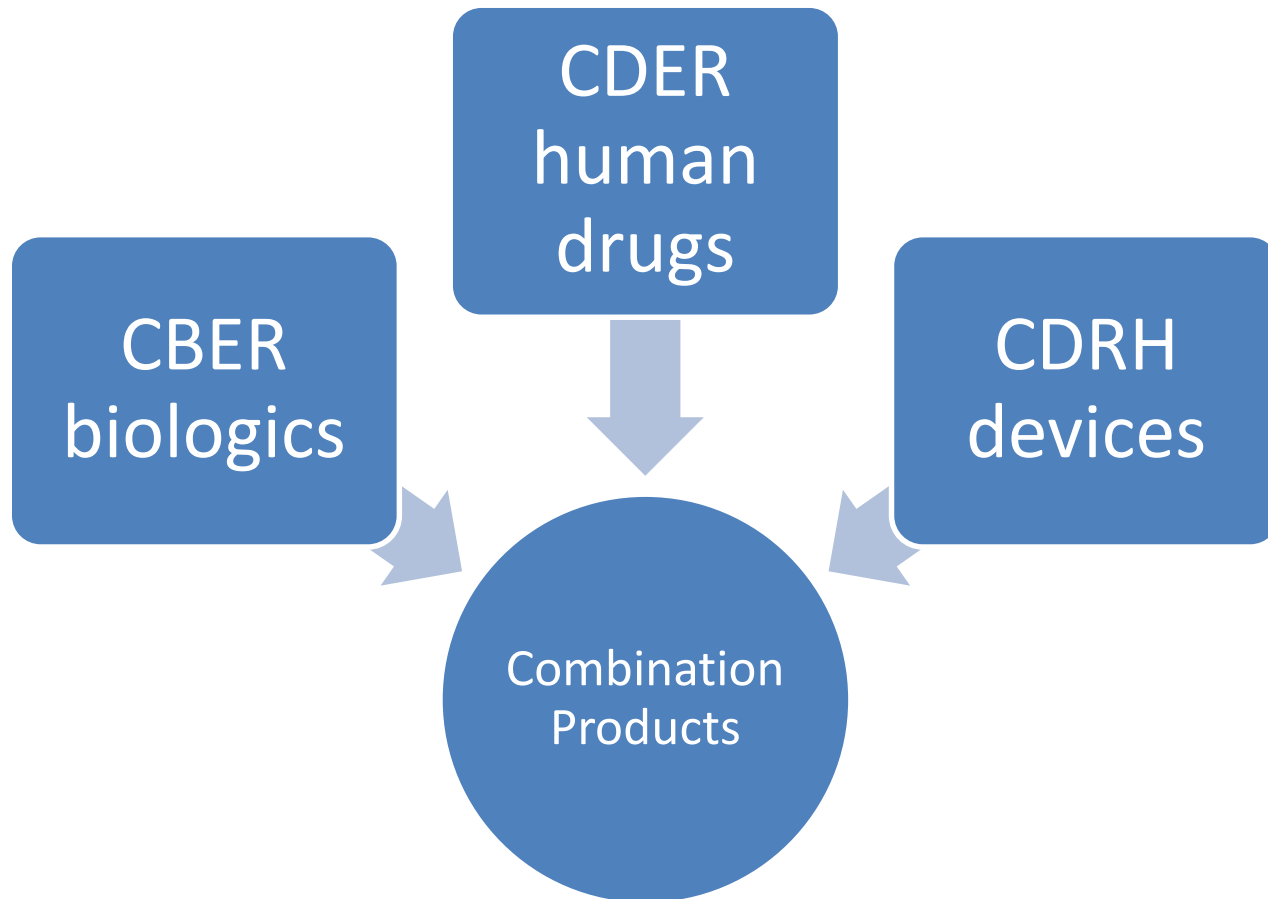
a drug and a biological product

a drug, device, and a biological product

Combination Products (cont.)

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 Coordination



Office of Combination Products

Office of Combination Products' primary responsibilities:

- ensure prompt assignment of combination products to FDA center (CDER, CBER, etc.)
- oversee 'timely and effective' premarket review
- oversee 'consistent and appropriate' postmarket regulation.

How are they regulated?

21 CFR Part 4 **Regulation of Combination Products**

- Drug products: 21 CFR parts 210 and 211
- Device part: 21 CFR part 820
- Biologics part: 21 CFR parts 600 – 680
- HCT/P component: 21 CFR 1271

Manufacturers subject to multiple CGMPs may follow a streamlined approach

Draft CGMP Guidance

- Draft guidance for industry, [Current Good Manufacturing Practice Requirements for Combination Products](#)
- What it is: general guidance
- What it is not: detailed analysis of any particular type or class of combination product
- Approach: address known areas of concern/confusion based on manufacturers' comments/input and agency experience

Online:

www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM429304.pdf

Points to Remember

Selection of CGMP operating system:

- Combination product manufacturers can choose whichever they prefer among 211-based streamlined approach, and 820-streamlined approach, or a non-streamlined approach
- Primary Mode of Action does not determine or dictate choice

Interacting with FDA:

- Generally work through lead center
- Office of Regulatory Affairs and inspections
- Contact Office of Combination Products as needed

US Code of Federal Regulation Requirements from Drug CGMPs

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

211 requirements

Testing and release for distribution (211.165)

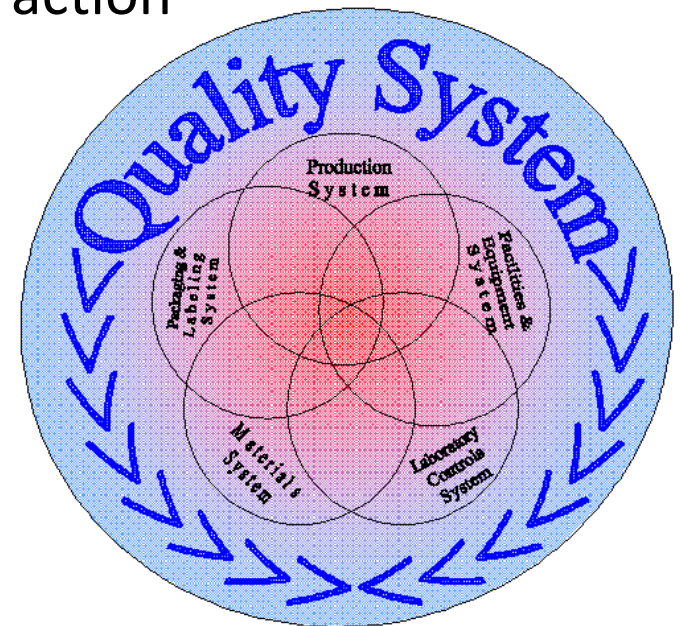
- Drug products must meet specifications, including **identity and strength**
- Drug product that doesn't meet specifications must be rejected

Special testing (211.167)

- **Sterility**, pyrogenicity, ophthalmic ointment specs, controlled-release
- Controlled-release combination products include drug-eluting stents and transdermal patches

Quality System Regulation Requirements

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



820 requirements

- Apply to combination products IF applicable to their device constituent parts
- “Convenience kits”: Must demonstrate compliance with CGMPs associated with kitting process (assembly, packaging, labeling, sterilization if any)
 - Convenience kits contain products that are:
 - Also legally marketed independently
 - Included in the kit as already packaged for independent marketing and with the same labeling as for independent marketing

820 requirements (cont.)

Design control (820.30)

- Applies to whole combination product, not just device constituent parts.
- Design history file can take many forms, including cross-reference to other records. Substantive content, not terminology, is the issue.
- Demonstrating compliance may just be a matter of organizing existing records.

Compliance

- Firms are inspected according to product type
- Combination product manufacturers should be inspected appropriately to reflect their manufacturing operations (e.g. drug and device inspection PACs, or just drug depending on the facility).

Case Study 1- Transdermal Patch

Undocumented/irreproducible test methods (211.165(e))

- Adhesion test conducted qualitatively
- Residue observed
- Unvalidated test methods (previous inspection too!)

Failure to justify deviations from laboratory control mechanisms (211.160(a))

- Didn't follow own procedure



Case Study 1 (cont.)

- Failed to investigate OOS (211.192)
 - Invalidated OOS without clear evidence of lab error
- Failed to maintain written records for evaluation at least annually (211.180(e))
 - Didn't look for trends in test results
- Failed to follow complaint handling and investigation procedures (211.198)
 - Failed to follow-up on consumer complaints
- Warning Letter, August 2016

Case Study 2- Atomizer & Refills

- Drug (refills) & Device (atomizer)
- Combination Product
 - Co-packaged
 - Refills only useful with device
- Unapproved new drug – did not meet OTC monograph
- Unapproved device – no 510(k) application
- Warning Letter 1
September 2013



Case Study 2 (cont.)

- Failure to investigate discrepancies (211.192)
 - Degradant in sterile inhalant
 - Decided on root cause without proper investigation
- Failure to follow stability testing program/to use those results to determine storage conditions and expiration dates (211.166(a))
 - Failed color and clarity, including 12-month stability
 - Waited 3 months to recall
- Warning Letter 2, September 2016

Summary

- Combination Products are regulated by CDER, CBER, and CDRH
- OCP helps determine the appropriate center(s) and assists with coordination
- Specific regulations must be met with a streamlined approach
- Firms are inspected according to product type

Thanks

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Questions?

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