Innovation in Combination Products

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Disclaimer

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Topics to be Discussed

- Revisiting the Definition for Combination Product as per 21 CFR Part 3
- What Is Not a Combination Product?
- Examples of Combination Products
- Premarket Approval and Product Overseeing
- Recent Clearances for Combination Products
- Applicable Regulations
- How to Comply with Applicable Regulations
- What Is Deferent from Other Commodity Inspections ?
- References

Revisiting the Definition for Combination Product as per 21 CFR

As defined on 21 CFR 3 *Combination Product* includes:

21 CFR 3.2(e)1

A **product comprised of two or more regulated components (products), 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.**

21 CFR 3.2(e)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.

Revisiting the Definition for Combination Product as per 21 CFR (cont.)

21 CFR 3.2(e)(3)

A drug, device, or biological product packaged separately for which **investigational plan or proposed labeling** indicates **use only with an approved individually specified drug, device, or biological product** and 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.

In other words, **Investigational New Drugs or Investigational Device Exemptions** which **are to incorporate an already approved drug, device, or biologic constituent**.

Revisiting the Definition for Combination Product as per 21 CFR (cont.)

21 CFR 3.2(e)(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.

In other words, **Investigational New Drugs or Investigational Device Exemptions** which **are to incorporate a drug, device, or biologic constituent also under investigational approvals.**

What Is Not a Combination Product

Combination products **are not:**

Products of the same classification, for example combination of drugs, devices or biologics integrated into a final product.

Drugs, devices or biologics which are otherwise combined or sold with other FDA regulated commodities such as food or cosmetics; **not intended to diagnose, treat, mitigate, or prevent illness or to alter any bodily structure.**

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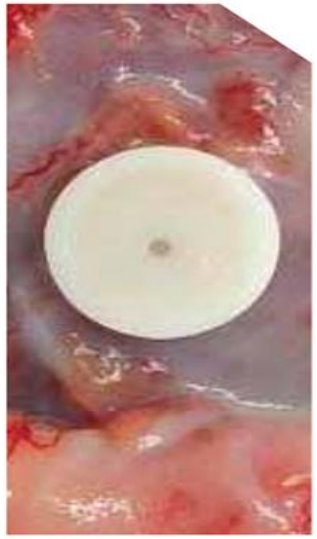
Examples of Combination Products

Prefilled Syringes

- Prefilled Auto injector
- (e.g Epinephrine, Insulin, Anti-Inflamatory)

Drug Coated Implantable Devices

- (e.g Cardiovascular Stents, Reconstructive Mesh, Cardiac Leads)



Implantable Drug Eluting Disks

- (e.g Localized Chemotherapy Disks)

Pre-market Approval and Product Overseeing

Mode of Action as it applies to combination products:

21 CFR 3.2(k)

Mode of action is the **means by which a product achieves an intended therapeutic effect or action**. For purposes of this definition, "therapeutic" action or effect includes **any effect or action of the combination product intended to diagnose, cure, mitigate, treat, or prevent disease, or affect the structure or any function of the body**.

Since combination products are comprised of more than one constituent device, drug or biologic product; it is understood that a products can present more then one mode of action.

Pre-market Approval and Product Overseeing (cont.)

The constituent which determines the most significant and “Primary Mode of Action” for the combination product will discern which center (CDER, CDRH, CBER..) will oversee premarket approval and inspectional assignments for the product. For example:

Drug Auto Injector Pen / Intended Use : Intended to Treat Anaphylaxis

Drug Constituent: Provides the therapeutic effect to prevent the life threating allergic reaction. **Primary Mode of Action**

Device constituent (auto injector): Enables the delivery of the drug. **Secondary Mode of Action**

Primary mode of action to achieve intended use is the drug constituent. Lead Center **CDER**

Pre-market Approval and Product Overseeing (cont.)

Device-Drug Combination Product

Cardiovascular Drug Eluting Stent / Intended Use: To Open an Artery

Device Constituent / Metallic Mesh Stent: To open artery. **Primary Mode of Action**

Drug Constituent / Anti-inflammatory: To prevent inflammation and restenosis. **Secondary Mode of Action**

Product will be overseen by Lead Center **CDRH**.

Recent Clearances

- Drug Eluting Sinus Stent
  - Re-absorbable polymer coated with drug.
  - Intended for mechanically maintaining patency after ethmoid sinus surgery.
    - Drug eluting capability to reduce the need for post-operative intervention as a result of adhesions and/or use of non-localized steroids.
- Artificial Embolization Device
  - Non-adhesive embolic agent comprised of drugs and devices.
  - Intended for pre-surgical embolization of brain arteriovenous malformation.
    - Allow for the selective occlusion of blood vessels.

Recent Clearances (Cont.)

- Bone Graft Material with Therapeutic Drug
  - Device / drug product indicated as an alternative to consecutive bone harvesting procedures.
  - Combines recombinant human platelet-derived growth factor with bio-absorbable synthetic material.

Applicable Regulations

Regulation Concerned with Combination Products

21 CFR Part 4

- Establishes which current good manufacturing practice requirements apply to these products; and provides a regulatory framework for designing and implementing the current good manufacturing practice “operating system” at facilities that manufacture co-packaged or single-entity combination products.

Applicable Regulations (Cont.)

- Reference is made under 21 CFR Part 4.2 to “operating system “ to safeguard compliance with applicable regulatory requirements.

- Post Market Surveillance Report requirements have been defined under Part B of the same regulation (21 CFR Part 4).

- The intended use, and “Primary Mode of Action” (PMOA) can serve as a premise for delineating a system which integrates manufacturing controls in order to fulfill requirements under applicable regulations.

Applicable Regulations (Cont.)

As before mentioned even when a Lead Center manages regulatory approvals and oversees regulatory inspections; this **does not imply that other constituents of the combination product will not be subjected to pertinent inspectional review for compliance with applicable regulatory requirements.**

Reference is made under 21 CFR Part 4 Section 4.4 “Under this subpart, for single entity or co-packaged combination products, compliance with **all applicable current good manufacturing practice requirements for the combination product** shall be achieved through the design and implementation of a current good manufacturing practice operating system.”

How to Comply with Applicable Regulations

- "Primary Mode of Action" (PMOA) as a premise for delineating a system which integrates manufacturing controls as per applicable regulations.

- Device/Drug product for which a device constituent provides the PMOA.
  - Establish a system to ensure compliance with Quality System Regulations for Medical Devices and complement with applicable portions of Drug cGMP's.

How to Comply with Applicable Regulations (Cont.)

- Drug / Device Product which a Drug constituent provides the PMOA.

  - Establish a system to ensure compliance with Drug cGMP's and complement with applicable portions of QS regulations.

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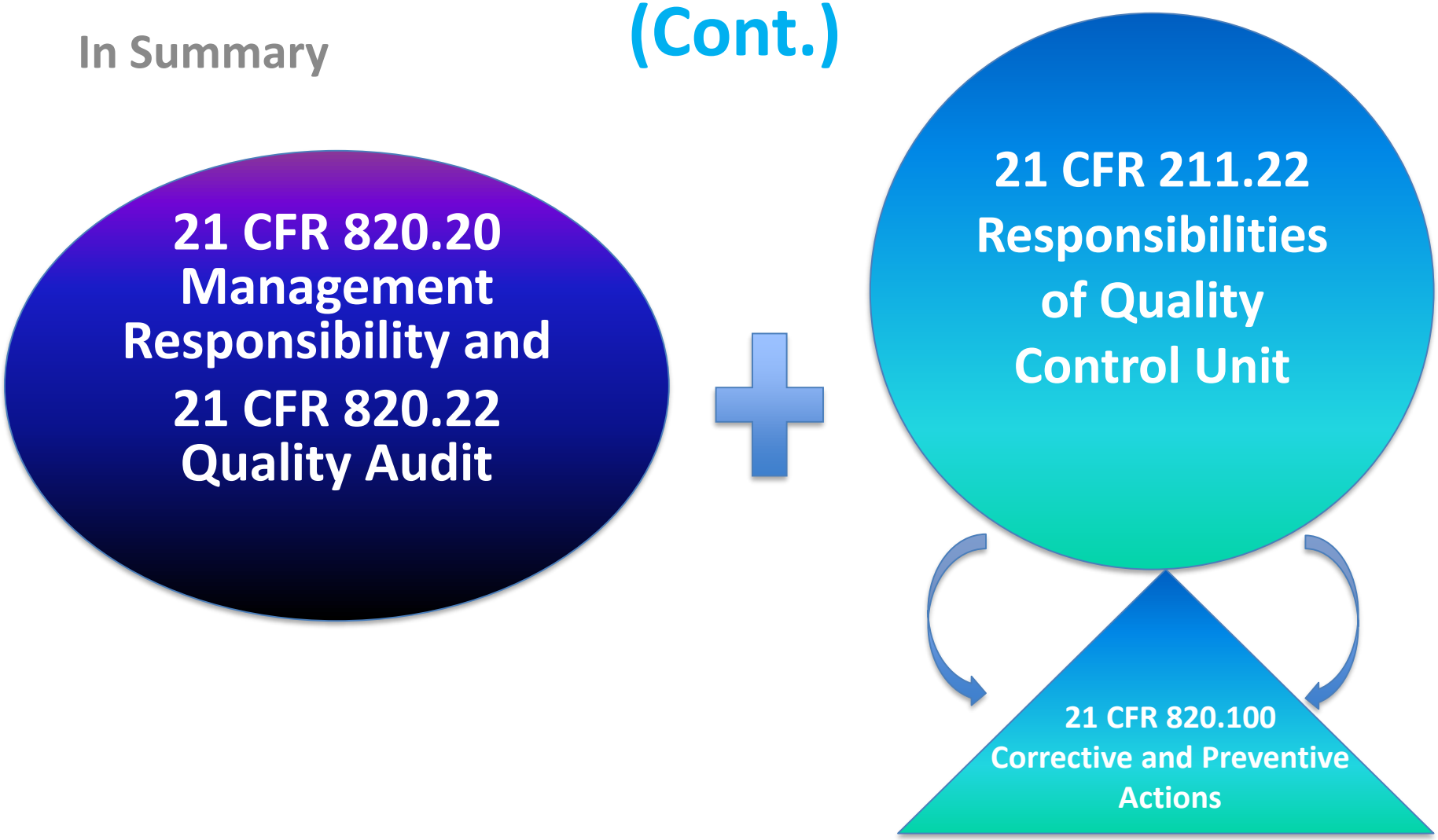
How to Comply with Applicable Regulations (Cont.)

In Summary



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How to Comply with Applicable Regulations (Cont.)

21 CFR 820.100 Non-conformities that rise from the failures in requirements to be accounted for as quality data sources in order to be escalated as needed into CAPA's

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21 CFR 211.84. Testing and approval or rejection of components, drug product containers, and closures.

Pre-determined as per 21 CFR 820.30 Design Controls

21 CFR 820.50 Purchasing Controls

How to Comply with Applicable Regulations (Cont.)

21 CFR 820.100 Non-conformities that rise from failures in requirements to be accounted for as quality data sources in order to be escalated as needed into CAPA's

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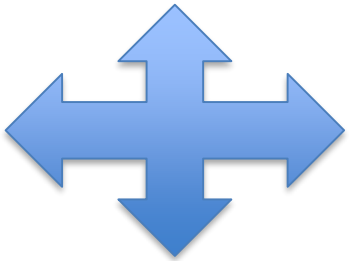
21 CFR 211.103 Calculation of yield
21 CFR 211.132 Tamper-evident packaging requirements / (OTC) human drug products
21 CFR 211.137 Expiration dating
21 CFR 211.165 Testing and release for distribution
21 CFR 211.166 Stability testing
21 CFR 211.167 Special testing requirements

Pre-determined as per 21 CFR 820.30 Design Controls



The method to measure during and after production should should be defined under Design Transfer activities.

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How to Comply with Applicable Regulations (Cont.)

Post-Market Surveillance Reports Requirements

- Regulation was last revised on **April 2018**.
  - Requirements and guidance has also adapted to newly revised rule.
- Guidance was published on its final form on 07/2019.
- The rule only applies to “Combination Product Applicants” and “Constituent Part Applicants” (as defined in Part 4.101).
- Does not apply to any other entities, investigational combination products, or to combination products that have not received marketing authorization.

How to Comply with Applicable Regulations (Cont.)

Post-Market Surveillance Reports Requirements

- "Combination Product Applicant"
  - The applicant that holds the only submission or all applications for a combination product.

- "Constituent Part Applicant"
  - The applicant that holds a submission for a constituent part of a combination product, the other constituent part(s) of which is marketed under an intended use held by a different applicant.

    - If the combination product is marketed by two different entities in a cross-labeled configuration. E.g a drug indicated for use with device; and a device indicated for use with a drug.

How to Comply with Applicable Regulations (Cont.)

- Application Type-Based Reporting Requirements.
  - Apply to *both "*Combination Product Applicants" and "Constituent Part Applicants", based on the application type under which the combination product or constituent part received marketing authorization. As per 21 CFR 4.102(b), Combination Product and Constituent Part Applicants who hold:
    - NDAs/ANDAs are subject to the safety reporting requirements described in 21 CFR Part 314.
    - BLAs are subject to the safety reporting requirements described in 21 CFR Parts 600 and 606.
    - Device Applications are subject to the safety reporting requirements described in 21 CFR Parts 803 and 806.

How to Comply with Applicable Regulations (Cont.)

Constituent Part-Based Reporting Requirements.

- Constituent part-based reporting requirements **apply *only* to Combination Product Applicants** and are based on the types of constituent parts included in the combination product.

- NDA/ANDA/BLA for a combination product that contains a device constituent.
  - Five-day reporting requirements (see 21 CFR 803.3, 803.53, and 803.56)
  - Malfunction reporting requirements (see 21 CFR 803.50 and 803.56)
  - Correction and removal reporting and recordkeeping requirements for events that do not require a report (see 21 CFR 806.10 and 806.20)

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How to Comply with Applicable Regulations (Cont.)

- BLA or Device Application for a combination product that contains a drug constituent part.
  - (21 CFR 4.102(c)(2)): o Field alert reporting (FAR) requirements (see 21 CFR 314.81)
  - Fifteen-day reporting requirements (see 21 CFR 314.80)

- ANDA/NDA or Device Application for a combination product that contains a biological product constituent part.
  - Biological product deviation reporting (BPDR) requirements (see 21 CFR 600.14 and 606.171)
  - Fifteen-day reporting requirements (see 21 CFR 600.8013)

How to Comply with Applicable Regulations (Cont.)

- Particular language on Part 4.102b(3) related to Combination Product Applicants and Constituent Part reports:
  - Unless you have already submitted a report in accordance with paragraph (c) of section 4.102, for the same event that: Includes the information required under the applicable regulations identified in this paragraph, is required to be submitted in the same manner under 4.104, and meets the deadlines under the applicable regulations identified in this paragraph.
  - In other words…if one report fulfills the requirements as the report for the constituent part and according to pre-market submission.

How to Comply with Applicable Regulations (Cont.)

Sec. 4.104 How and where must you submit postmarketing safety reports for your combination product or constituent part?

(a) If you are a constituent part applicant, you must submit postmarketing safety reports in accordance with the regulations identified in 4.102(b) that are applicable to your product based on its application type.

(b) If you are a combination product applicant, you must submit postmarketing safety reports required under 4.102 in the manner specified in the regulation applicable to the type of report, with the following exceptions:

- (1) You must submit the postmarketing safety reports identified in 4.102(c)(1)(i) and (ii) in accordance with 314.80(g) of this chapter if your combination product received marketing authorization under an NDA or ANDA or in accordance with 600.80(h) of this chapter if your combination product received marketing authorization under a BLA.
- (2) You must submit the postmarketing safety reports identified in 4.102(c)(2)(ii) and (c)(3)(ii) in accordance with 803.12(a) of this chapter if your combination product received marketing authorization under a device application.

How to Comply with Applicable Regulations (Cont.)

Given the recent revision of PMSR Rule and published guidance, it is encouraged to contact the FDA's Office of Combination Products to better discern an adequate course of action for post-market reports.

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What Is Different from Other Commodity Inspections

- Reasonable expectation for team inspections.
- Multiple citations applicable to constituent parts on same 483.
- Annotations for device citations.
  - Promised to Correct
  - Promised to Correct by X
  - Promised to Correct Within X
  - Reported Corrected, Not Verified
  - Reported Corrected and Verified
    - Investigator's discretion
  - Under Consideration
  - No Annotation
- Additional Request for Information from multiple Centers (CDR, CDRH, CBER).

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References

- 21 CFR Part 3

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=3

- 21 CFR Part 4 Subpart A and B

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=4

- **Current Good Manufacturing Practice Requirements for Combination Products Guidance for Industry and FDA Staff January 2017**

- **Postmarketing Safety Reporting for Combination Products Guidance for Industry and FDA Staff *FINAL GUIDANCE July 2019***

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Questions