Combination Products
Regulatory Updates and Inspection Trends

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Objectives

• Definition of CPs
• Why CPs?
• History of Combination Product regulations
• FDA Requirements
• Compliance Approach
• Compliance Challenges for Companies
• FDA Enforcement
• Recommendations
What is a CP?

Defined in 21 CFR 3.2(e):

- A product composed of two or more regulated components (i.e., any combination of a drug, device, or biological product) that combined or mixed and that which produces a single entity;
- Two or more separate products packaged together in a single package or as a unit and comprised of any combination of a drug, device, or biological product;
- 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
- 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.
What is a combination product?

“Constituent part”: A drug, device, or biological product that is part of a combination product. See 21 CFR 4.1
What is a CP?

- **Final rule on CGMP** requirements for combination products applies to all combination products.
- **Preamble to the final rule**, the CGMP requirements for constituent parts of cross-labeled combination products that are manufactured separately and not co-packaged are the same as those that would apply if these constituent parts were not part of a combination product (e.g., for a drug/device combination product, 21 CFR parts 210 and 211 would apply to the manufacture of the drug constituent part(s), and 21 CFR part 820 would apply to the device constituent part(s)).
Why CPs?

• Emerging technologies are being combined in ways that merge engineering, chemistry, and biology.

• CP companies are creating some exciting new products on the market and present new opportunities for device companies. Examples:
  • Contact lenses that contain drugs for treating glaucoma
  • Implanted cell lines for treating Insulin Dependent Diabetes, Parkinson’s Disease and Alzheimer’s Disease.
  • Pre-filled syringes and auto-injectors offer convenience and improved safety for patients and healthcare workers
Types of CPs

- **Fully Integrated** – a single unit where constituents cannot be separated (e.g. drug patch)

- **Partially Integrated** – constituents are separate with the device part often reusable (e.g. auto-injector pens refilled with cartridges containing drug solution)

- **Non-integrated** – two constituents that do not really work together (e.g. surgical kit containing Lidocaine, gauze, scalpels, etc.)
Examples of CPs

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. e.g.: Monoclonal Antibody combined with a therapeutic drug; pre-filled syringe; drug-eluting stent; condom with spermicide; MDIs; transdermal patches; etc.
Examples of CPs

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. For examples: drug or biological product packaged with a delivery system; surgical tray with surgical instruments, alcohol pads, etc.
Examples of CPs

A drug, device, or biological product packaged separately that according to its 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.

Photosensitizing Drug/Laser Light Activated Drug (e.g. Photodynamic therapy (PDT), a light-activated treatment for cancer and other diseases). PDT utilizes light-sensitive drugs or photosensitizers that can be preferentially localized in malignant tissues.
History of CPs?

• Combination Products officially recognized as a new entity in 1990 in the Safe Medical Devices Act.
• April 2002 – FDA created Office of Combination Products (OCP) to assess new CP submissions and assign them to best OR most appropriate “Lead” Center.
• June 2003, 21 CFR Part 3 became effective describing Center assignment for CP's.
• DRAFT Guidance for Industry on CGMP Requirements for Combination Products published January 2015.
What are the FDA Requirements for CPs?

• Constituent parts retain their regulatory status (drug, device, biologic) after they are combined.
• GMP requirements for each constituent part must also be met when combined.
• A manufacturer can choose to operate under either streamlined approach (211 or 820 based) regardless of the types of premarket authorizations they are seeking.
• The CP sponsor is responsible for ensuring that the manufacturing activities for its product occurs at all facilities, including facilities operated by third parties, are in compliance with CGMP requirements.
FDA Requirements of CPs

Two options for demonstrating GMP compliance identified for Single Entity and Co-Packaged Combination Products

1. Manufacturer of CP must demonstrate **full** compliance with applicable regulations for each constituent

2. Streamlined Approach – Manufacturer is compliant with drug or medical device cGMP requirements AND

   Manufacturer must meet specified sections from the other set of cGMP regulations
What does this mean?

• If a company only manufactures one of the constituents (e.g. drug or device or biological) – they are required to only meet the appropriate regulations for that product (21 CFR 211 or 820 or 600), respectively.

• If a company (site) manufactures BOTH constituents, they must meet both sets of regulations

• If constituents are manufactured separately then shipped to another site where they are joined chemically or physically, then that site must meet Part 4 requirements and the Streamlined Approach may be used.
## CGMPs for Different Types of Combination Products

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| **Examples**                     | • Certain light-emitting devices and light-activated drugs  
• Certain imaging devices and imaging agents | • First-aid or surgical kit                           | • Drug-eluting stent                                  
• Syringe packaged with vial of drug              | • Prefilled syringe                                   
• Toothbrush packaged with toothpaste            | • Transdermal patch                                  
• Bone void fillers with drugs                  |                                                       |
| **Reference**                    | 21 CFR 3.2(e)(3), (4)                                 | 21 CFR 3.2(e)(2)                                      | 21 CFR 3.2(e)(1)                                      |

If a facility is only manufacturing one constituent part of a cross-labeled product, they are only subject to the CGMPs applicable to **that type** of article (e.g., drug CGMPs if article is a drug). See 78 FR 4308
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**Streamlined approach** is available under 21 CFR 4 to comply with drug and device CGMP requirements.
Streamlined Compliance

If the primary constituent is a drug, manufacturer must also meet specified Medical Device (21 CFR Part 820) requirements:

- **Section 820.20**: Management responsibility
- **Section 820.30**: Design controls
- **Section 820.50**: Purchasing controls
- **Section 820.100**: Corrective and preventive action
- **Section 820.170**: Installation
- **Section 820.200**: Servicing
Streamlined Compliance

If the primary constituent is a device, manufacturer must also meet specified Drug (21 CFR Part 211) requirements:

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

- Biological products, including those that are constituent parts of combination products, must comply with all applicable requirements in parts 600 through 680.

- Note:
  A biological product is always also regulated as either a drug subject to the drug CGMP regulations (21 CFR 210/211) OR A device subject to the QS regulation described in 21 CFR part 820.
  As appropriate, regardless of whether the biological product is a constituent part of a combination product.
HCT/P CGTPs

• If a combination product includes an HCT/P, Current Good Tissue Practices (CGTPs) for HCT/Ps under 21 CFR part 1271 must be met as applicable.
• Refer to 1271.10 and 1271.20 when considering what regulations apply to a combination product with an HCT/P constituent part.

See “Guidance for Industry; Current Good Tissue Practice (CGTP) and Additional Requirements for Manufacturers of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)” (http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM285223.pdf)
Lead Center Role

A combination product is assigned to an agency center that will have primary jurisdiction for that CP’s premarket review and regulation.

Under section 503(g)(1) of the FD&C Act, the assignment of a CP to the center with primary jurisdiction is based on determination of which constituent part provides the primary mode of action (PMOA) for the CP.
Lead Center

- FDA’s OCP makes decision on which Center should be assigned jurisdiction based on the CP PMOA.
- PMOA (Primary Mode of Action) definition: “the means by which a product achieves a therapeutic effect.” Manufacturer must submit (and OCP agrees or decides) which mode of action (MOA) contributes the greatest effect on the MOA.
- Sometimes a difficult decision:
  - e.g. Drug-eluting stent – assigned to CDRH
  - e.g. Drug-eluting disc with chemotherapeutic agent for cancer treatment – assigned to CDER
Center Assignment

• Some CPs are not easily classified:
  ➢ APPLIGRAF Wound Dressing (by Organogenesis) used to treat serious skin wounds caused by venous insufficiency. It consists of a scaffold dressing structure containing bovine collagen, human keratinocytes and fibrocytes from human infant foreskin. Despite the cellular constituents, FDA assigned this to CDRH
  ➢ Encapsulated cell lines and drugs inside an implantable capsule assigned to CBER based on PMOA.

• Inter-Center agreements permit consultation between centers for review of CPs on an as needed basis.
Center Assignment

• If PMOA is not determined by the manufacturer, they can submit a “Request for Designation” to FDA who will assign new CPs to the Center regulating similar products or to the Center with the most expertise on safety and efficacy.

• OCP has 60 days from acceptance of new product submission to decide on PMOA and Center to be assigned.
CP numbers

In 2007, there were 333 applications to OCP, of which:
- 142 classified as CDER lead
- 148 as CDRH lead
- 43 as CBER lead
- All applications met applicable time frames.

In 2014 there were 310 applications:
- 155 classified as CDER lead
- 43 classified as CBER lead
- 111 classified as CDRH lead
- Additional 1013 requests for consultation from CDER
- Nearly all met applicable time frames
What are some Challenges?

• Reporting of Adverse Events may require MDR and/or Drug (or Biologic) Adverse Event reporting. No clear guidance yet on this topic.

• While drug and medical device regulations are very similar in philosophy, they differ significantly in how to document and perform certain activities.
Challenges

• Co-packaged CP manufacturers, including manufacturer of kits, must assess the impact of any sterilization process on the items in the co-package.
  
  - A constituent part may be sensitive to further processing or sterilization. Testing must be performed to confirm no degradation in safety and effectiveness. In addition, complete validation of the sterilization process should be done to insure sterility for each constituent part within the kit.
Challenges for Device Companies?

- **Section 211.84**: Testing and approval or rejection of components, drug product containers, and closures
  - Device companies do not typically have labs to perform analytical testing on drug products and components
  - Kit manufacturers purchase commercially available, ready to use drugs and see no need to test the product
- **Section 211.103**: Calculation of yield
  - Many complex, implantable devices are individually made and essentially have a lot size of one.
Challenges for Device Companies?

• **Section 211.137: Expiration dating**
  - Labeling of convenience kits contain a single expiry date for the kit, which likely differs from the expiry printed on the drug label

• **Section 211.166: Stability testing**
  - Device companies do not have laboratory facilities or ability to perform testing; may not understand lot and testing requirements

• **Section 211.170: Reserve samples**
  - Reserve samples are supposed to be kept inside their packaging configuration for the expiry period. The numbers required (by CDER) may be extremely expensive or large in size (dimension).
Challenges for Drug Companies?

• **Section 820.20**: Management responsibility regulations
  - Requirements are more specific and require senior management reviews and assurance that management is knowledgeable/participates in decisions involving quality systems and manufacturing controls

• **Section 820.30**: Design controls
  - Required for all device components. Since devices are frequently purchased or outsourced, drug companies must ensure design qualification documents are complete and up to date. (Risk assessments, controls for risks identified and human factor testing – part of design controls.)
Challenges for Drug Companies?

- **Section 820.50: Purchasing controls**
  - Device requirements based on documented risk and assessment of supplier’s ability to deliver quality product
  - Applicable to component/device manufacturers AND service providers, consultants, other vendors

- **Section 820.100: Corrective and Preventive Action**
  - Primary process for devices in recognizing, investigating and correcting quality issues reported through deviations, complaints, audits, change control, manufacturing controls, etc.
  - Relies heavily on **trending** and statistical analysis in the Medical Device industry.
  - Investigation of event or issue is part of CAPA rather than a separate deviation system.
Regulatory Actions

Warning Letter issued in January 2014 on pre-filled syringe product with auto-injector and vial reconstitution adapter (Biological Combination Product)

- Warning Letter written for device constituents
  - Failure to establish, implement and follow design validation procedure (820.30(g))
  - Failed to fully assess and validate changes to device design prior to implementation (820.30(i))
  - Failed to properly assess qualifications of a supplier/vendor/service provider (820.50(a))

- Per the W/L – FDA expects CP regulations to be retrospectively met for legacy products that predate the Part 4 enforcement date (July 22, 2013).

- Bottom Line: All products prior to the rule should have complied with CGMPs. CGMPs pre-existed before the Rule.
Recommendations

• Drug/Device/Biologic companies should conduct Gap analyses to determine if constituents in a combination product continue to be safe and effective.
• Drug/Device/Biologic companies should have appropriate auditors to identify gaps in regulations. Auditors should have the appropriate expertise in each area.
• FDA Draft guidance has been challenging in addressing the multiple issues involving the many types of drugs, devices, biologics and CP’s involved.
• When in doubt, contact the lead Center, OCP, and/or ORA.
• On the web: www.fda.gov/combinationproducts/default.htm
Recommendations

Drug / Device / Biologic company that submits the application has ultimate responsibility for ensuring compliance with the CP rules and regulations.

• Manufacturers are currently subject to inspection to 21 CFR 4 requirements.

• Make sure your company is informed and educated regarding CP rules and regulations.

• In absence of pressing public health concerns, FDA will work with manufacturers if they work with us, to resolve compliance issues, before taking further action (e.g., issuing warning letters)

• Companies should not be caught off guard when FDA starts enforcing regulations.
References

- 21 CFR 210/211 – cGMPs for Drugs
- 21 CFR 820 – QS Regulation for Devices
- 21 CFR 600 – 680 for Biologics
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QUESTIONS