Applying Good Manufacturing Practices to Combination Products

Presented by

Elizabeth Griffin
Medical Device Specialist
U.S. Food & Drug Administration
New England District

Monday June 4, 2012
AFDO Conference
Providence, RI

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

Objectives

- Definitions
- Examples
- Regulations
- Additional Information

What is a Combination Product?

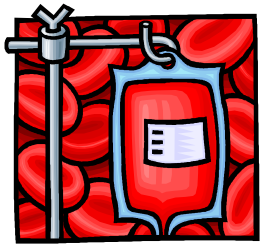
A combination product is a product composed of any combination of:

- a drug and a device;
- a biological product and a device;
- a drug and a biological product; or
- a drug, device, and a biological product

Definitions

- Biological Product
- Drug
- Medical Device

Biological Product



A virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product … applicable to the prevention, treatment or cure of a disease or condition of human beings

PHS Act Section 351(i)

Drug

(A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and

(B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and

(C) articles (other than food) intended to affect the structure or any function of the body of man or other animals

FD&C Act Section 201(g)

Device

An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which:

(1) is recognized in the NF, USP, or supplement to them,

(2) is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or

(3) is intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body and which is not dependent upon being metabolized for the achievement of its primary intended purposes.

FD&C Act Section 201(h)

What is a Combination Product?

A product composed of any combination of:

- a drug and a device;
- a biological product and a device;
- a drug and a biological product; or
- a drug, device, and a biological product

21 CFR Part 3.2(e)

FD&C Act Section 503(g)

A Combination Product includes:

1. Two or more regulated components that are physically, chemically, or otherwise combined or mixed and produced as a single entity;

2. Two or more separate products packaged together in a single package or as a unit;

3. A drug, device, or biological product packaged separately that … 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 …, or

4. Any investigational drug, device, or biological product packaged separately that … 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.

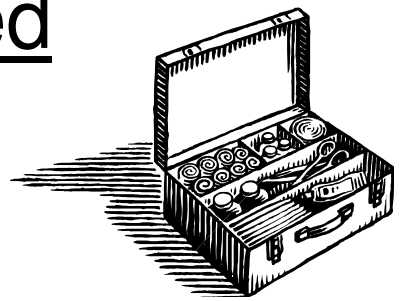
Examples of Combination Products

Where components are physically, chemically or otherwise combined:

- Drug-eluting stent
- Condom with spermicide
- Prefilled syringes
- Metered dose inhalers
- Insulin injector pens
- Transdermal patches

Examples of Combination Products

Where components are packaged together:

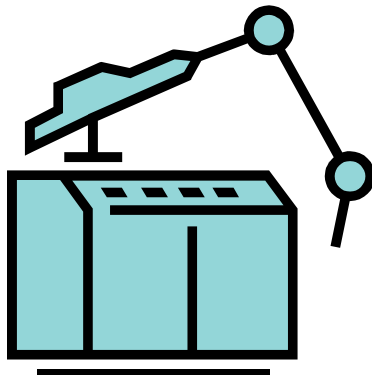


- Drug or biological product packaged with a delivery device
- Surgical tray with surgical instruments, drapes, and lidocaine or alcohol swabs

Examples of Combination Products

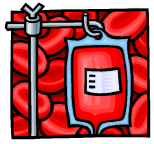
Where components are separately provided but labeled for use together:

- Photosensitizing drug and activating laser/light source



Regulatory Authorities

Combination products are comprised of components that, individually, would usually be regulated by separate Centers under different types of regulatory authorities



- *Biologics* are regulated by the Center for Biologics Evaluation and Research (CBER),

- *Drugs* are regulated by the Center for Drug Evaluation and Research (CDER), and

- *Medical Devices* are regulated by the Center for Devices and Radiological Health (CDRH)

Primary Jurisdiction

- The lead center for the investigation of a combination product is determined by the primary mode of action (PMOA)
- PMOA = The single mode of action of a combination product that provides the most important therapeutic action of the combination product
- The Office of Combination Products (OCP) assigns the lead center (CBER, CDER or CDRH)
- The applicant may submit a Request for Designation to OCP for determining the lead center if there is no precedent.

Request for Designation

- Brief description of product & its major components
- A description of its intended use, clinical/therapeutic claims, including types of patients it will be used for
- Its modes of action
- Any other relevant information

FDA Regulations

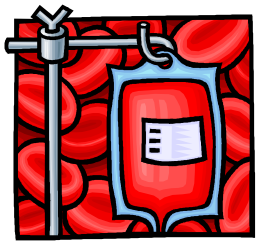
- GMPs: Good Manufacturing Practices
- For Drugs, Devices and Biologics
- cGMPs: Current Good Mfg Practices
- Quality System (QS) Requirements for Devices

What cGMP requirements apply to my combination product?

- cGMPs in parts 210 & 211 apply to combo products with a drug constituent part
- cGMPs in part 820 apply to combo products with a device constituent part
- cGMPs in part 606 apply to combo products with blood & blood components
- cGMPs in other parts in 600-680 apply to combo products with applicable biological products constituents
- Current Good Tissue Practices and Donor Eligibility Requirements in part 1271 apply for human tissues

How can I comply?

Compliance with all applicable cGMP requirements for each product



Similar Requirements

- There is considerable overlap in the drug and device regulations.
- Both require management, organization, personnel, documentation, & record keeping
- Both allow flexibility in manufacturing

Specific Requirements

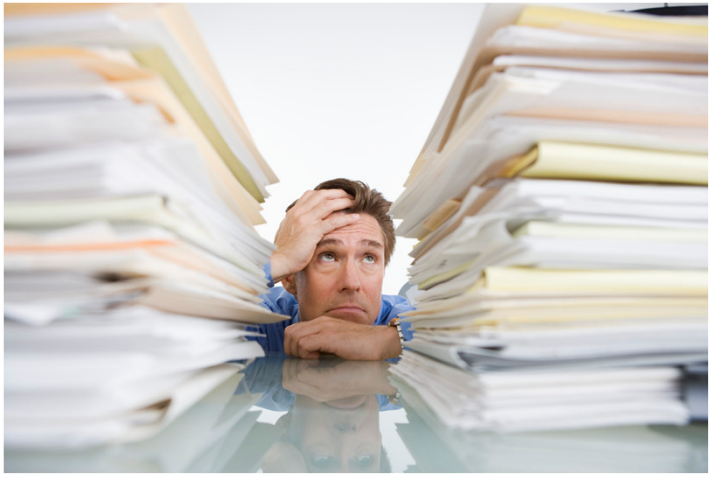
- Each set of regulations contains certain specific requirements.
- Drugs: stability and yield requirements
- Devices: Corrective and Preventive Action (CAPA) requirements
- Biologics: donor eligibility and infectious disease testing requirements

Regulations

- FDA has not promulgated cGMP regulations specifically for combination products.
- Until it does so, each constituent part is subject only to its governing cGMPs when marketed separately.

Regulations

For combination products which are combined or co-packaged, both sets of regulations apply after joining the constituent parts together.



One Manufacturing System

- Based on the PMOA
- Consider specific requirements of the other manufacturing system

Table 1: Key Current Good Manufacturing Practice Provisions to Consider During and After Joining Together Co-packaged and Single-Entity Combination Products

If the Operating Manufacturing Control System is Part 820 (QS Regulation)		If the Operating Manufacturing Control System is Part 210/211 (CGMP Regulation)	
Carefully Consider These Specific CGMP Requirements	Title	Carefully Consider These Specific QS Requirements	Title
§ 211.84	Testing and approval or rejection of components, drug product containers, and closures	§ 820.30	Design controls
§ 211.103	Calculation of yield	§ 820.50	Purchasing controls
§ 211.137	Expiration dating	§ 820.100	Corrective and preventative actions
§ 211.165	Testing and release for distribution		
§ 211.166	Stability testing		
§ 211.167	Special testing requirements		
§ 211.170	Reserve samples		
* Including all subsections, as appropriate.			

Where to go for More Information

- Draft guidance document: *Current Good Manufacturing Practices for Combination Products (9/2004)*
- Federal Register Proposed Rule dated 9/23/2009: *Current Good Manufacturing Requirements for Combination Products*
- OCP Website: www.fda.gov/CombinationProducts

Guidance Documents

- The Office of Combination Products has several draft guidance documents posted on the FDA website
- Links to a variety of guidance documents developed by CBER, CDER, and CDRH that might be of interest to combination product manufacturers are also available

Questions?