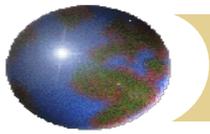


# *Combination Products Regulation in the United States*

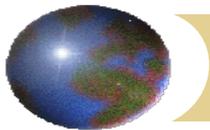
*Presenter:*

Scott Sardeson RAC US/EU  
3M Health Care  
St. Paul, MN USA



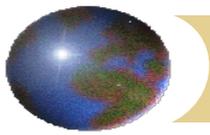
# Presentation Outline

- ✦ Combination products
  - ✦ Definitions and Regulations
  - ✦ Jurisdiction
- ✦ Premarket Review
  - ✦ Lead Center Assignment
- ✦ Postmarket Oversight
- ✦ General Goals & Considerations for establishing regulatory controls
- ✦ Resources



# *What is a Combination Product*

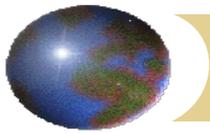
- ❖ Combinations of drugs, devices, and/or biological products (not combinations of same type, e.g., drug with a drug)
- ❖ Types include:
  - ❖ Chemically or physically combined products (e.g., drug-eluting stents, patches, or implants; prefilled auto-injectors or syringes, metered dose inhalers)
  - ❖ Co-packaged products (e.g., first-aid kits; surgical kits)
  - ❖ “Cross-labeled” products (e.g., photosensitizing drug and activating light source labeled specifically for use with one another)
- ❖ Legal nature = that of the constituent parts “plus.”
- ❖ No U.S. statutory or regulatory standards specifically for combination products.



# *Definition of Drug*

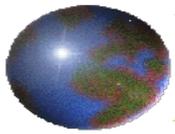
The term "drug" means:

- (A) articles recognized in the US Pharmacopoeia, Homeopathic Pharmacopoeia, or National Formulary;
  - (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals;
  - (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals.
- ✦ 21 USC 201(g)



# Definition of Device

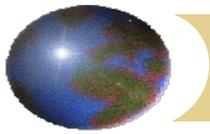
- ❖ Instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other **similar or related article, including any component, part, or accessory, which is -**
  - ❖ (1) recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them
  - ❖ (2) 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) 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 of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.**
- ❖ 21 USC 201(h)



# *Definition of Biological Product*

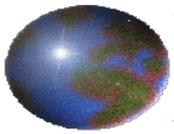
The term "biological product" means [in pertinent part]:  
a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), **or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.**

✚ 42 USC 262



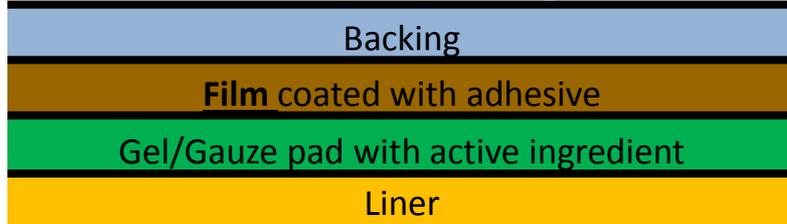
# Who Regulates?

- ✦ In US the lead center is defined by the Primary Mode of Action (PMOA)
- ✦ The lead center assignment can be from one of the following:
  - ✦ Center for Drug Evaluation and Research (CDER)
  - ✦ Center for Devices and Radiological Health (CDRH)
  - ✦ Center for Biologics Evaluation and Research (CBER)
- ✦ Example:
  - ✦ Drug eluting stent or wound dressing with antimicrobial – typically a device (CDRH)
  - ✦ Asthma inhaler or medicinal patch – typical a drug (CDER)



# Example of PMOA

## Pad with Drug



Device

## PMOA = Wound dressing

- Protects IV site or wound
- Absorb fluid
- Localized effect of drug
- 21 CFR 820 Quality System Regulation

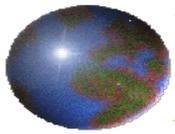
## Adhesive with Drug



Drug

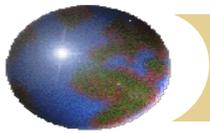
## PMOA = Drug Delivery

- Delivers drug dosage over time
- Pharmacological effect
- Systemic affect of drug
- 21 CFR 211 GMP



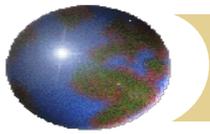
# *Office of Combination Products*

- ✦ The US FDA Office of Combination Products (OCP) is a statutorily mandated office
  
- ✦ The role of the OCP is as follows:
  - ❑ Classifies and assigns therapeutic products for regulation
  - ❑ Coordinates and oversees regulation of combination products
  - ❑ Resource for industry



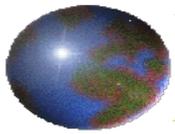
# Coordination

- ✦ SOP for inter-center consultation process developed by OCP with Centers:
  - ✦ Consults same priority as assigned products
  - ✦ Consultation/collaboration as needed
  - ✦ OCP actively monitors
- ✦ OCP available informally and formally to both sponsors and review staff
  - ✦ Facilitate meetings
  - ✦ Help resolve product class and product specific combination product concerns
  - ✦ Help resolve disputes between Centers or with sponsors



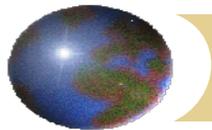
# *Policy & Practice Development*

- ❖ OCP works with CBER, CDER, CDRH, and other agency components as appropriate to establish and clarify regulatory approaches and pathways
  - ❖ Inter-center coordination in the US FDA
  - ❖ Reviewer tools and training
  - ❖ Inter-center working groups
  - ❖ Internal memoranda of understanding and standard operating procedures
  - ❖ Guidance and regulations of combination products



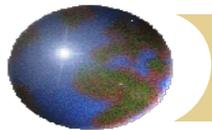
# Combination Product Concepts

- ✦ US FDA has three key concepts it uses in the regulation of combination products
  1. Constituent parts retain regulatory status and duties
  2. Combination products are a distinct regulatory class
  3. Comprehensive, effective oversight without undue redundancy



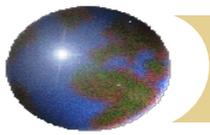
# *Classification of constituent parts*

- ✦ “Drug” & “intended” effects (21 USC 321(g))
- ✦ “Device” & “chemical action” (21 USC 321(h))
- ✦ “Biologic” & “analogous product” (42 USC 262(i))
- ✦ Lead Center assignment (21 CFR Part 3)
  - ✦ Primary Mode of Action (PMOA)
  - ✦ Algorithm and previous decisions that have set precedence
  - ✦ Process is data and claims driven
  - ✦ Request for Determination (RFD) process is available for “gray” areas
    - Binding with 60-day decision deadline



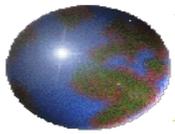
# *Application Process*

- ✦ Lead Center Assignment – Who will be primary Center for the product?
- ✦ Investigational Application - Is it necessary and if so what is required?
- ✦ Marketing Application - What path will be used for product clearance or approval?
- ✦ Coordination – How will the US FDA manage the information internally?



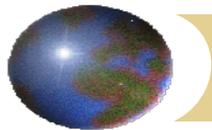
# *Lead Center Assignment*

- ✦ Primary mode of action (PMOA) standard define Lead Center
  - ❖ Greatest contribution to overall intended therapeutic effect of the combination product
  - ❖ Data and claims based analysis
- ✦ Algorithm for when PMOA unclear (e.g., when constituent parts provide distinct therapeutic effects)
  - ❖ Step 1: Does a Center already regulate combination products raising similar questions of safety and effectiveness?
  - ❖ Step 2: If not, which Center has the most expertise regarding the most significant questions of safety and effectiveness for the combination product?



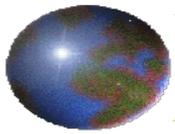
# *Product Characteristics*

- ✦ What is new or different, e.g.,
  - ✦ Inclusion of drug that is a new molecular entity
  - ✦ New indication, area of use/exposure
  - ✦ Different drug formulation or device modification
  - ✦ Change in dosing
  - ✦ Complexity or new science/technology
  - ✦ New population, new risks



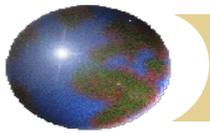
# *Investigational Application*

- ✦ Generally only one investigational application if necessary
  - ✦ Not all combination product require IDE applications – for example products using well known medicinal ingredients such as antimicrobial agents
- ✦ Protocol review and initial review of data by Centers
- ✦ Include all information for all constituent parts
- ✦ Milestone meetings include both Centers, all key manufacturers, OCP as appropriate



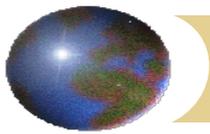
# Premarket Review Process

- ✦ The Conformity Assessment is done by the US FDA Centers
  - ✦ Based on Safety and Effectiveness—constituent parts & interaction of constituent parts
  - ✦ Combined/coordinated analysis and decision-making by Centers, with OCP input as needed
- ✦ Varying pathways to market depending on technology and PMOA
- ✦ Consistent procedure and standards to review process



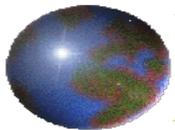
# Marketing Application

- ✦ Once submitted the product application has a coordinated review by Centers
  - ❖ Generally only one marketing application needed
  - ❖ If two are appropriate (may be the case for cross-labeled combination products), authorize marketing only when/if both are ready for approval/clearance
- ✦ Facility inspections by staff is conducted with appropriate expertise for all constituent parts
  - ❖ Strong business relationships can be essential, e.g., to ensure success
  - ❖ Ongoing reliance on proprietary data
  - ❖ Appropriate coordination of post marketing changes to constituent parts



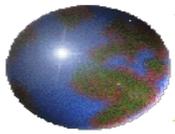
# *Drug—Device Issues*

- ✦ Some considerations relating to device constituent parts:
  - ❖ Leaching/extraction of materials into the drug/biologic substance.
  - ❖ Changes in stability of the drug constituent when delivered by a device or when used as a coating on a device.
  - ❖ Drug adhesion/absorption to the device materials that could change the delivered dose.
  - ❖ Device actions that could affect drug/biologic performance characteristics.
  - ❖ Drug interactions with device material that could alter the material's characteristics/functionality.
  - ❖ Need for human factors study when appropriate (e.g., auto-injectors).



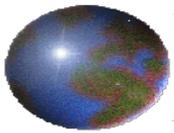
# *Use of Existing Data*

- ❖ Demonstrating safety and effectiveness while avoiding unnecessary clinical study—some options and considerations:
  - ❖ Data master file/cross reference to third-party's approved marketing application for proprietary data
    - Completeness of rights of reference
    - Relevance of data
  - ❖ Existing clinical studies under FDA investigational applications
    - Broadened indication or intended target population
    - New route of administration or use in new area of body
    - Change in design or formulation that may affect safety or effectiveness
    - Rights of reference



# *Use of Existing Data Cont'd*

- ✦ Further options and considerations:
- ✦ Foreign studies not conducted under FDA investigational applications
  - ✦ Validity of data, compliance with Declaration of Helsinki
  - ✦ Applicability to US population and medical practice
- ✦ Literature
  - ✦ Completeness of study documentation
  - ✦ Availability of raw data
- ✦ Bridging studies



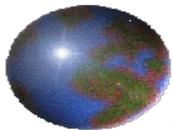
## *Example 1: Approved drug and new device use*

### ✦ Scenario:

- ✦ Drug X is a topical cream approved to treat disease A.
- ✦ Device Y is a light source cleared for a different use
- ✦ New combination product combines Drug X with Device Y for photodynamic treatment to enhance drug effect for treatment of disease A

### ✦ Data needs

- ✦ Do not need to reprove that Drug X treats disease A
- ✦ No need to show that Device Y can activate Drug X and to determine what, if any, dose changes are needed to ensure safety and effectiveness of combined use to treat disease A.



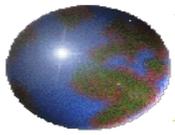
## *Example 2: New molecular entity for combined use with device*

### ✦ Scenario:

- ✦ Investigational combination product combines an investigational topical cream Drug X with Device Y for photodynamic treatment for treatment of disease A

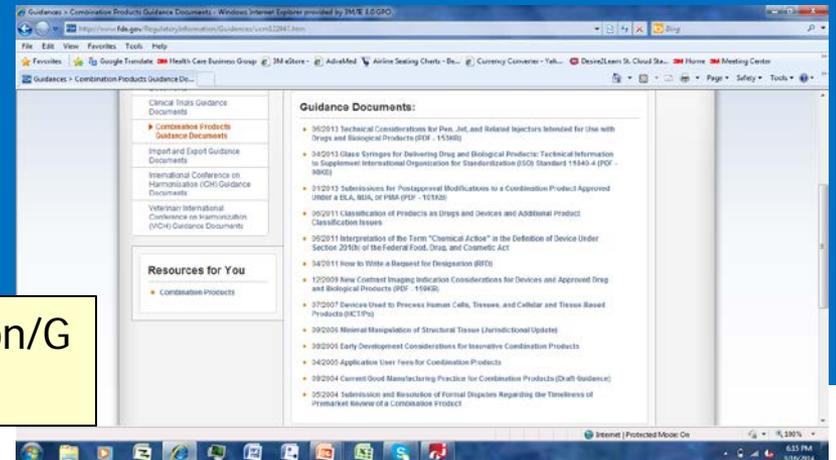
### ✦ Data needs

- ✦ Need to prove that Drug X treats disease A
- ✦ Need to show that Device Y can activate Drug X and determine appropriate dose to ensure safe and effective combined use to treat disease A.

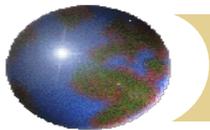


# Post Market Guidance Documents

- 01/2013 Submissions for Postapproval Modifications to a Combination Product Approved Under a BLA, NDA, or PMA (PDF - 101KB)
- 06/2011 Classification of Products as Drugs and Devices and Additional Product Classification Issues
- 09/2004 Current Good Manufacturing Practice for Combination Products (Draft Guidance)



<http://www.fda.gov/RegulatoryInformation/Guidances/ucm122047.htm>



# Q. System Requirements

⊕ Co-packaged or single-entity combination product

⊕ If the combination product includes a device constituent part and a drug constituent part, and the current good manufacturing practice operating system has been shown to comply with the drug cGMPs, the following provisions of the QS regulation must also be shown to have been satisfied:

21 CFR 820.20. Management responsibility.

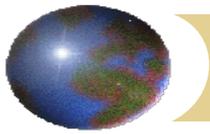
21 CFR 820.30. Design controls.

21 CFR 820.50. Purchasing controls.

21 CFR 820.100. Corrective and preventive action.

21 CFR 820.170 Installation and/or 21 CFR 820.200 Servicing, where the combination product or constituent part would have hardware requiring such installation and/or servicing.\*\*\*

\*\*\*This was not identified in the 2004 Combination Product GMP Draft Guidance document but current thinking is that this may be necessary

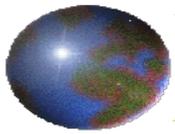


# Q. System Requirements

## ✦ Co-packaged or single-entity combination product

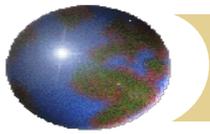
If the combination product includes a device constituent part and a drug constituent part, and the current good manufacturing practice operating system has been shown to comply with the QS regulation, the following provisions of the drug cGMPs must also be shown to have been satisfied:

- 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 211.137. Expiration dating.
- 21 CFR 211.132. Tamper-evident packaging requirements for over-the-counter (OTC) human drug products.
- 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.



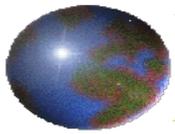
# *General Goals & Considerations*

- ✦ US FDA has some general goals and considerations in the regulation of combination product
  - ✦ Consistency, coordination, clarity
  - ✦ Agency SOPs, training, guidance, information technology
  - ✦ Value of an independent coordinating body between Centers
  - ✦ Building upon existing systems v. creating a new one
    - Submissions (NDA, PMA, 510K, IDE)
    - Quality Systems and GMP
    - Adverse Event Reporting
- ✦ Very helpful to industry also in order to assure predictability



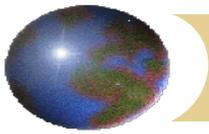
# *General Considerations & Factors*

- ✦ These require establishing
  - ✦ Sound, consistent review standards
  - ✦ Appropriate expertise
  - ✦ Timely review
  - ✦ OCP duty to ensure timely effective premarket regulation
  - ✦ Statutory authority to use all agency resources



# Observations

- ❖ Some of the lessons the US FDA has learned are
  - ❖ Coordination and application of consistent, appropriate, review standards is important
  - ❖ Systemic drivers and establishing new procedures and duties for combination products
  - ❖ Evolving process and guideposts
  - ❖ Value of independent coordinating body



✦ Many thanks to the following for information in this presentation from slides they presented previously

John Barlow Weiner, Esq.  
Associate Director for Policy  
Office of Combination Products  
US Food and Drug Administration

Kimberly A. Trautman  
Associate Director, International Affairs  
Office of the Center Director  
Center for Devices and Radiological Health