Combination Products: A Regulatory Perspective

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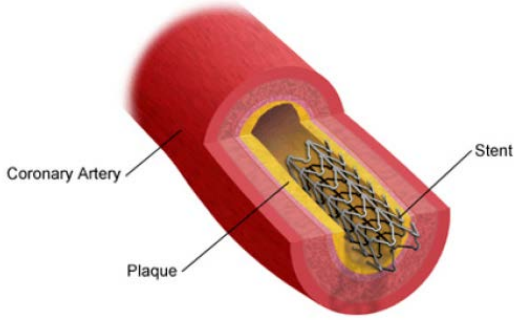
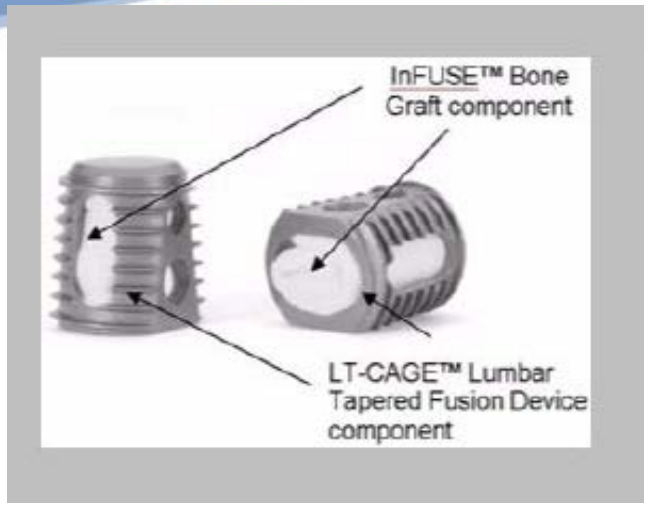
Outline

- Combination Products
- Jurisdiction
- Regulatory Challenges
- Regulations/Guidance for Industry
- Human Factor Studies
- Comparability
- Case Studies

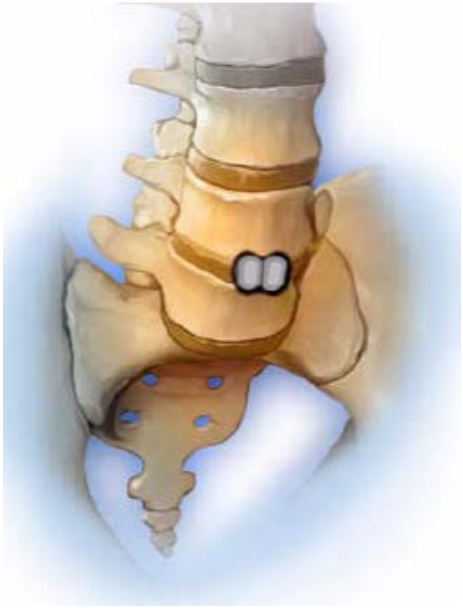
Examples

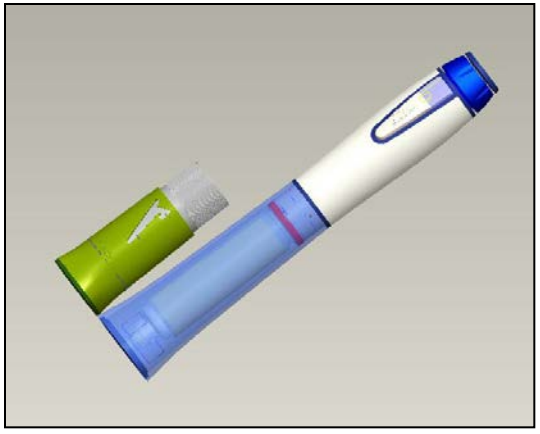
Stent Inside a Coronary Artery





Implanted InFuse™ Product





Injector Pen

Dental Implant

Prefilled Syringes

- In 2005 the worldwide market for pre-filled syringe was ~ 1 billion units in 2010 that number has increased to over 2 billion units
- The growth of the market is anywhere from 12.5% to 20% yearly.[1]

[1]Ondrugdelivery.com 2005

Prefilled Syringes

- Advantages
  - Ease of administration
    - Easier for patients to use at home or in emergency situations
  - Prefilled dosage reduces medication errors
  - Elimination of vial overfill
  - Greater assurance of sterility
  - Cost

Prefilled Syringes

- Disadvantages
  - Technical challenges for developing and manufacturing
    - Silicone
    - Aggregates
    - Leachable and Extractable
  - Regulatory challenges
  - Greater cost of development

Jurisdiction

Who Has Jurisdiction?

- Governed by Primary Mode of Action (PMOA)
  - 21 CFR 3.2m
  - Primary mode of action is the therapeutic action that is expected to make the greatest contribution to the overall intended therapeutic effect of the combination product.
  - Whichever product has the greatest therapeutic effect, the center that the product is regulated in will have jurisdiction.

Who Has Jurisdiction?

- Drug eluting stent - CDRH - PMOA is the stent opening the artery
- Drug eluting disks - CDER - PMOA is the cancer chemotherapy
- Bone graft substitutes – CDRH and CDER
  - CDRH lead – PMOA is spinal or fracture stabilization
  - CDER lead – device component acts as drug delivery system

Request for Designation (RFD)

- 21 CFR 3.7
- Ask for classification (biologic/device) and Center lead assignment
  - Primary mode of action (PMOA)
  - Similarity to other regulated products
  - Center with most experience/expertise
- Fully voluntary
- Guidance Document: How to Write a Request for Designation

Request for Designation (RFD)

- The request is submitted to the Office of Combination Products (OCP)
  - Each center will review the RFD and write a short memo agreeing or disagreeing with the sponsor
  - OCP will make final determination

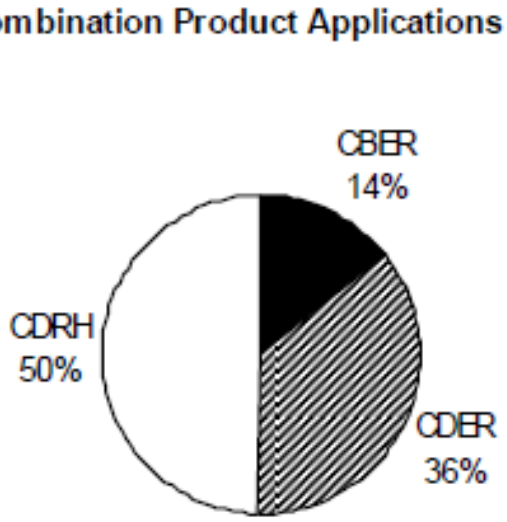
- FDA has 60 days to make the decision

Office of Combination Products

- Mandated by the Medical Device User Fee and Modernization Act of 2002 (MDUFMA)
- Works with industry and CBER, CDER and CDRH
- Make jurisdictional determinations
- Oversee/help coordinate premarket review and ensures consistent/appropriate postmarket regulation
- Develops policy, guidance and regulations
- Serve as resource for industry and review staff

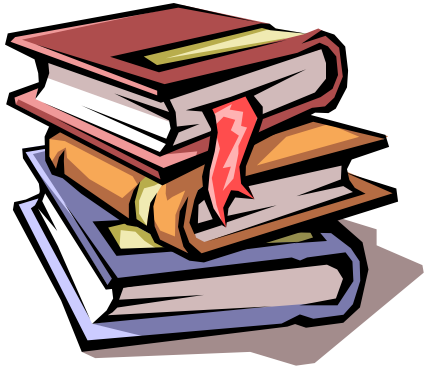
Combination Products By the Numbers

- Total of 311 submitted to the Agency in 2010 (latest data)
- Highest percentage are INDs and 510Ks
- 32 RFD were assessed



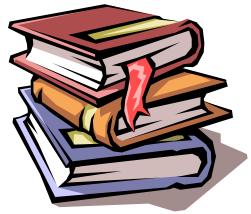
http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/PerformanceReports/CombinationProducts/UCM270772.pdf

Regulatory Challenges



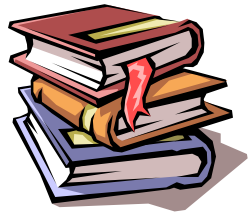
General Regulatory Differences

- Each Center has a different set of laws and regulations acting as the basis for its authority
  - Food, Drug and Cosmetic Act
    - Drugs and Devices
  - Public Health Services Act
    - Biologics
  - Code of Federal Regulations (21 CFR)
    - 314 Drug
    - 600 Biologics
    - 800 Device



General Regulatory Differences

- Any available laws or regulations may be applied as necessary and appropriate for regulation of specific combination product
  - This will change as new regulations are promulgated



General Regulatory Differences

- Least Burdensome provisions of the FDA Modernization Act do not apply to the complete combination product
  - only apply to the device component(s)

General Regulatory Differences

Each Center is organized differently

CDER/CBER

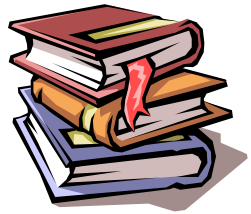
clinical	pharm/tox	CMC	manufacturing	compliance

CDRH

device issues clinical pharm/tox CMC	manufacturing and compliance

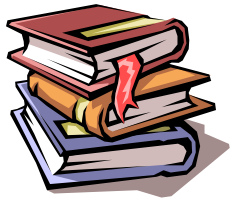
Specific Regulatory Differences

- Electronic submissions
- Meetings
- Clinical studies
- Non-clinical studies
- Marketing applications
- Manufacturing and compliance



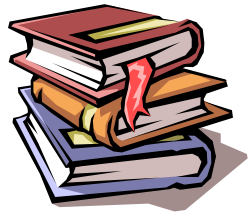
Electronic Documents

- CDER/CBER
  - electronic submissions generally required
  - accessible by CDRH
- CDRH
  - optional electronic submissions
  - accessible by CDER/CBER



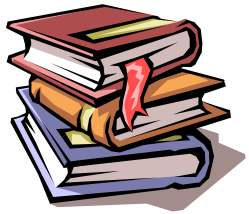
Regulatory Meetings

- CDER/CBER
  - Type A, B or C
  - Formal processes
  - 30, 60, 75 day
- CDRH
  - pre-submission
    - informal
    - 60 day clock
  - “regular” request
    - informal
    - first available date
  - Agreement
    - formal
    - 30 day clock



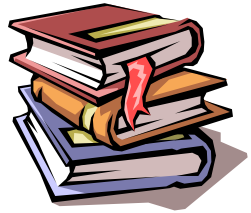
Clinical Studies: CDER/CBER

- Investigational New Drug (IND)
  - Phase 1
    - Primarily Safety and to determine pharmacologic and metabolic activity and side effects
    - Exempt from CGMPs
  - Phase 2
    - Often dose-finding studies
    - Study efficacy in a limited group of individuals
  - Phase 3
    - Used to evaluate overall benefit-risk relationship of the drug
    - Provide adequate basis for physician labeling
- Clinical Hold



Clinical Studies: CDRH

- Investigational Device Exemptions (IDE)
  - Feasibility
  - pilot
  - pivotal
  - Exempt from QSRs
- Number of required studies product-dependent
- No direct mapping to IND phases
- No concept of clinical hold
- Need to demonstrate “relative safety” prior to initiation
- Max 30 day review cycle



Non-Clinical Studies

- Types of data is the same between Centers but the timing of data and conditions for initiating clinical trials are different

- CDER/CBER
  - specific upfront data submission with commitments for subsequent data submissions during studies
- CDRH
  - all necessary data submitted upfront as part of "relative safety" demonstration
  - usually no additional data submitted after approval

Original Applications

Lead Center	Application Type	Review Clock
CDER/CBER LEAD	New Drug Application or Biologic License Application	6 Month (Priority Review) Or 10 Month (Standard Review)
CDRH	Pre Market Approval	180 Day
	510K premarket notification	90 Days
	HDE humanitarian device exemption	75 Days

Manufacturing Changes: Post Licensure

- Changes to Manufacturing Process
- New Facility
- Changes to Sterilization
- Extension of Expiration Date
- Changes in Equipment, Raw Materials, New Master or Working Cell Bank
- Change in Methods
- Change in device design

Manufacturing Changes: Post Licensure

- CDER/CBER
  - 21 CFR 314.70
  - 21 CFR 601.12
- CDRH
  - 21 CFR 814.39(a)
  - 21 CFR 814.39(b)
  - 21 CFR 814.39(f)

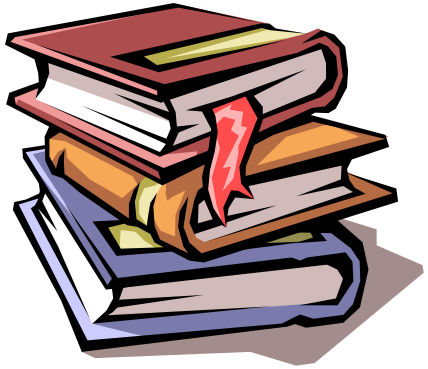
Manufacturing Supplements

Lead Center	Manufacturing Supplement	Review Clock
CDER/CBER LEAD	Prior Approval	4 Months
	Changes Being Effective	6 Months
	Annual Report	1 Year

Manufacturing Supplements

Lead Center	Manufacturing Supplement	Review Clock
CDRH	PMA Supplement	180 Days
	30-Day Notice and 135-Day PMA Supplement	30 Days or 135 Days
	Annual Report	90 Days
	HDE Supplement	30 Days or 75 Days

Regulations and Guidance Documents



Manufacturing Practices

- Which should you follow?
  - There are currently no CGMPs/QS regulations for combination products
  - Each constituent part (drug, device or biologic) will be regulated under their cGMP/QSR requirements when manufactured separately and later combined
  - For combination products produced as a single-entity or co-packaged both sets of cGMP/QS regulations are applicable

Manufacturing Practices

- Draft Guidance for Industry: Current Good Manufacturing Practice for Combination Products (2004)
- Manufactures of combination products should meet with the FDA and discuss how the CGMP/QSR requirements apply to their product throughout product development

Gaps in CGMPs and Quality System Regulations

21 CFR 820.20	Management Responsibilities	Some overlap with ICH Q10 and CGMPs
21 CFR 820.30	Elements of Design	Some overlap with ICH Q8
21 CFR 820.50	Purchasing Controls	Overlaps with CGMPs but has explicit requirements
21 CFR 820.100	CAPA	Overlaps with CGMPs but has explicit requirements
21 CFR 820.170	Installation	
21 CFR 820.200	Servicing	

Gaps in CGMPs and Quality System Regulations

21 CFR 211.84	Testing and approval of DP container closures
21 CFR 211.103	Calculation of yield
21 CFR 211.132	Tamper-evident packaging for OTC
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
21 CFR 211.170	Reserve Samples

Federal Register Notice

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 4

[Docket No. FDA–2008–D–0409]

Current Good Manufacturing Practice Requirements for Combination Products

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA or agency) proposes to codify the current good manufacturing practice (cGMP) requirements applicable to combination products. This proposed rule is intended to promote the public health by clarifying which cGMP requirements apply when drugs, devices, and biological products are combined to create a combination product. In addition, the proposed rule sets forth a transparent and streamlined regulatory framework for firms to use when demonstrating compliance with cGMP requirements for ''single-entity'' and ''co-packaged'' combination products.

Proposed 21 CFR 4

- Subpart A – Current Good Manufacturing Practice Requirements for Combination Products
  - The proposed rule at 4.4(b) would offer two options for demonstrating compliance with cGMP requirements for each of the constituent parts in *co-packaged or single-entity combination product*.
    - (1) To demonstrate compliance with the specifics of all cGMP regulations applicable to each of the constituent parts
    - (2) To demonstrate compliance with the specifics of either the drug cGMPs or the QS regulation, rather than both

Proposed 21 CFR 4

- 4.4(b)(1):
  - If you follow the drug cGMP regulations at 21 CFR 210 and 211, you must also follow specific provisions of the QS regulation,
    - § 820.20. Management responsibility
    - § 820.30. Design controls
    - § 820.50. Purchasing controls
    - § 820.100. Corrective and preventive action
    - § 820.170. Installation
    - § 820.200. Servicing

Proposed 21 CFR 4

- 4.4(b)(2)
  - If you follow the drug QS regulations at 21 CFR 820, you must also follow specific provisions of the cGMP regulations
    - § 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

Guidance for Industry

- Guidance for Industry and FDA Staff - Early Development Considerations for Innovative Combination Products (2006)
- FDA Guidance: Container Closure Systems for Packaging Human Drugs and Biologics (May 1999)
- DRAFT Guidance for Industry: Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products (2009)
- Variety of ISO standards are also useful

Human Factor Studies

Human Factor Studies

- Changing regulatory landscape
  - These are now required instead of “nice to do”
  - Relying on controlled clinical studies will not substitute for Human Factor Studies
- Human Factor Premarket Evaluation Team is part of CDRH Office of Device Evaluation
  - Collaborates with CDER’s Division of Medication Errors Prevention and Analysis

Human Factor Studies

- Guidance for Industry and FDA Staff: Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management (2000)
- Draft Guidance for Industry and FDA Staff: Applying Human Factors and Usability Engineering to Optimize Medical Device Design (2011)

Human Factor Studies

- Formative Usability Testing
  - Identifies strengths and weaknesses
  - How can it be made better
  - Should be conducted while device is still under development
  - Iterative Process
- Summative Usability Testing
  - Final product testing
  - Tested by representative user under realistic conditions
  - Develop mitigation strategy for failures or problems that arise
    - Modify the design interface
    - User instructions/training
    - Re-test to show effectiveness of mitigation

Most Common Human Factor/Usability Review Concern[1]

- HF/Usability work is needed but not provided
- No HF/Usability work prior to summative/HF Validation testing
- Discovering new use-related problems at this point and “explaining them away”
- Lack of effective follow up on residual risk and performance failures
- Related hazards not identified

[1]Adapted from Ron Kay, Molly Follette Story, QuynhNhu Nguyen FDA/CDRH/ODE September 20, 2011

Most Common Human Factor/Usability Review Concern[1]

- Inadequate or absent description or characterization of errors
- No systematic collection of subjective description by test participants
- Not testing with representative users of the intended population of users
- Testing and evaluation not clearly related to tasks

[1]Adapted Ron Kay, Molly Follette Story, QuynhNhu Nguyen FDA/CDRH/ODE September 20, 2011

Product Concerns

Understanding the Impact of the Device on the Well Characterized Protein

Product Concerns

- Consider how the product will be used in the clinic
  - Length of mixing and holding time prior to implant
- Assess the key product quality attributes using release and characterization assays
  - Purity
  - Protein recovery
  - Specific activity
  - Glycosylation
- Understanding the interaction between the device and the biologic or drug

Demonstration of Comparability: Vials to Prefilled Syringes

Comparability

- Not uncommon for products to be developed initially in vials (liquid/lyophilized) and then switched to prefilled syringes
  - Ideally the switch should occur prior to the pivotal clinical studies
  - Need to demonstrate comparability between vials and prefilled syringes
    - The extent of comparability is dependant on the phase of development
    - Now subject to combination product regulations

Demonstration of Comparability

- Biocompatibility testing should be performed as described in Use of International Standard ISO-10993, Biological Evaluation of Medical Devices Part-1: Evaluation and Testing (May 1995)
- Need to determine if the current formulation is compatible with the prefilled syringe
  - Silicone can interfere with the protein or exicipients in the drug product

Demonstration of Comparability

- Demonstrate that the prefilled syringes do not impact product quality using Release and Characterization tests
  - Potency
  - Purity
  - Aggregation
  - Include impurity profiles where applicable
  - Glycosylation
  - Deamidation
  - N-terminal truncation
  - Secondary, tertiary, quaternary structure

Demonstration of Comparability

- Conduct leachable and extractable studies for all component materials for the device
  - Full description of extraction procedures should be described
  - Leached tungsten has been an issue for some proteins
- Comprehensive stability testing should be conducted in the prefilled syringes to establish expiration dating.
  - Bench testing for container closure and package ruggedness should include
    - Mechanical reliability
    - Pressure changes
    - Vibrations
    - Temperature cycling and temperature extremes
  - Shipping studies should be performed with the drug product in prefilled syringes

Demonstration of Comparability

- Preclinical or clinical studies may be required depending on the impact to product quality
  - The extent of preclinical or clinical studies depends on phase of development
- Other Considerations
  - Human Factor studies
  - Confirm that all applicable regulations are being followed

Case Studies

Case Study #1

- New IDE
- Licensed Biologic with a new matrix
- Matrix is a combination of a known material and additional component
- Sponsor performed elution studies
  - Found the biologic was completely oxidized
    - Sponsor demonstrated that potency was not affected
- IDE was Disapproved
- Did not provide data showing if other attributes may have been impacted using release and characterization assays
  - Did not provide a rationale on why the oxidation occurred

Case Study #2

- Pre-filled Syringes
  - Impact: tungsten salts caused protein oxidation followed by aggregation
  - Up to 60% of aggregated product found in some syringes
- Resolution (different approaches were used by different Sponsors)
  - Optimal - switch to platinum instead of tungsten filaments
  - Alternative – establish tungsten specifications, nitrogen overlay process, special washing procedure, etc.

Summary

- Regulation of Combination Products are complex
- Identification of appropriate regulations is often difficult and confusing but new regulations should be prorogated soon (target date: May 2012) to help eliminated the confusion
- Human Factor studies are required for prefilled syringes Important to study the impact the device has on the biologic/drug component
- Comparability studies not only include product impact but the impact of the product on the device
- Early contact/collaboration with the FDA is recommended to reduce development time and expenses

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