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

Injector Pen

Implanted InFuse™ Product

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

¹Ondrugdelivery.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

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

<table>
<thead>
<tr>
<th>Lead Center</th>
<th>Manufacturing Supplement</th>
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</tr>
</thead>
<tbody>
<tr>
<td>CDER/CBER LEAD</td>
<td>Prior Approval</td>
<td>4 Months</td>
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<tr>
<td></td>
<td>Changes Being Effective</td>
<td>6 Months</td>
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<td></td>
<td>Annual Report</td>
<td>1 Year</td>
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</tbody>
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<tbody>
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<td>180 Days</td>
</tr>
<tr>
<td></td>
<td>30-Day Notice and 135-Day PMA Supplement</td>
<td>30 Days or 135 Days</td>
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<td>90 Days</td>
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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


• 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

<table>
<thead>
<tr>
<th>21 CFR 820.20</th>
<th>Management Responsibilities</th>
<th>Some overlap with ICH Q10 and CGMPs</th>
</tr>
</thead>
<tbody>
<tr>
<td>21 CFR 820.30</td>
<td>Elements of Design</td>
<td>Some overlap with ICH Q8</td>
</tr>
<tr>
<td>21 CFR 820.50</td>
<td>Purchasing Controls</td>
<td>Overlaps with CGMPs but has explicit requirements</td>
</tr>
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<td>21 CFR 820.100</td>
<td>CAPA</td>
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<td>21 CFR 820.170</td>
<td>Installation</td>
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<td>21 CFR 820.200</td>
<td>Servicing</td>
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Gaps in CGMPs and Quality System Regulations

<table>
<thead>
<tr>
<th>21 CFR</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>21 CFR 211.84</td>
<td>Testing and approval of DP container closures</td>
</tr>
<tr>
<td>21 CFR 211.103</td>
<td>Calculation of yield</td>
</tr>
<tr>
<td>21 CFR 211.132</td>
<td>Tamper-evident packaging for OTC</td>
</tr>
<tr>
<td>21 CFR 211.137</td>
<td>Expiration Dating</td>
</tr>
<tr>
<td>21 CFR 211.165</td>
<td>Testing and Release for distribution</td>
</tr>
<tr>
<td>21 CFR 211.166</td>
<td>Stability Testing</td>
</tr>
<tr>
<td>21 CFR 211.167</td>
<td>Special Testing Requirements</td>
</tr>
<tr>
<td>21 CFR 211.170</td>
<td>Reserve Samples</td>
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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 4

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


- 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 Concern¹

- 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

¹Adapted from Ron Kay, Molly Follette Story, QuynhNhu Nguyen FDA/CDRH/ODE September 20, 2011
Most Common Human Factor/Usability Review Concern¹

- 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

¹Adapted 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 excipients 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
Acknowledgement

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