Unveil the Myth about Validation of Combination Products (21 CFR part 4)

Leonel Vanegas
Director Quality Engineering
October 29, 2015
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Agenda

- Benefits of Combination Products
  - Value Proposition for Combo products
  - Common Myths - When Parma met Devices
  - Primary Mode of Action (PMOA)

- Development of Combination Products
  - Understanding combo product life cycle
Agenda

- Design Validation and Process Validations
  - Usability and Human Factors studies
  - Difference between drug vs. device equipment validations
  - Consideration for drug vs device process validations
  - Risk Management Harmonization

- Challenges in compliance and Corporate Culture
  - Readiness for FDA pre-approve inspections (PAI)
  - Preventing FDA-483s or Warning letters
  - Change Management

- Q&A
Biosimilars

Biologics

Generics

Technology

Company

Devices

Drugs

Compliance
Combination Technologies

• Innovated products, usually exceeding customer expectations.
• More attractive for cost-effectiveness and easy of use.
• Combine two or more technological inventions
• Solve current pressing challenges in regulated industries.
Agenda

- Benefits of Combination Products (WHY?)
  - Value Proposition for Combo products
  - Common Myths -When Parma met Devices
  - Primary Mode of Action (PMOA)
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Benefits and Value Proposition

- **Financial**
  - Long term patient care reducing healthcare costs
  - High growth potential with profit margins

- **Healthcare**
  - Increase patient compliance
  - Reduce systemic side effects and adverse events
  - Enable local delivery, increasing effectiveness/efficacy

- **Technology**
  - Competitive advantage (ANDAs/510ks).
Definition of Drug

- (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… or other similar or related article, including any component, part, or accessor,” which is -

- (1) 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
- (2) intended to affect the structure or any function of the body of man or other animals,

“Does not achieve its primary intended purposes through chemical action within the body…which is not dependent upon being metabolized for the achievement of its primary intended purposes.” 21 USC 201(h)
Combination Products

- Diagnostics and therapeutic products
- Due to 21CFR part 4 in 2013, FDA expects more combo filings every year.
- Technological advances, competitive market, and healthcare reforms are drivers to develop combo product for home use vs. hospital or Doctor’s use.
- Combo products blurs the historical lines of jurisdiction or separation from all three FDA centers (CBER, CDER, and CDRH). OCP born in 2002.
Combination products

Device/Drug

Device/Biologic

Biologic/Drug

Device/Drug/Biologic

A product composed on one of these combinations
Combination Products

- Single Entity
  - Drug Eluting Stent

- Co-Package
  - Syringe packaged with drug in vial

- Cross Labeled
  - Light activated cancer drug
Common Myths

- Same as “Fixed Combination Products or combination packs” (e.g. drug/drug, device/device)
- Regulated by Office of Combination Products (OCP)
- Final Rule (21 CFR part 4) not applicable yet
- Drug and/or device validations are separate
- Legacy commercial products out of scope
- OUS Manufacturing sites, suppliers and CMOs are exempt
When Parma Met Devices
Healthcare Product History

Drugs: ~50yrs
Biologics: ~30yrs
Devices: ~25yrs
Brief History of combination products

- Safe Medical Device Act of 1990 – combination products first statutorily recognized
  - Require alignment to lead center based on Primary Mode of Action (PMOA)

- Office of combination products (OCP)
  - Created by Medical Device User Fee and Modernization Act (MDUFMA) 2002
  - Given broad oversight covering life cycle of combination products
  - Coordinate reviews among three centers (CBER/CDER/CDRH)
  - Ensures consistency in regulatory reviews
Primary Mode of Action

- OCP facilitates designation for PMOA
  - Mode of action (MOA)= means by which a product achieves a **therapeutic effect** or action (21CFR 3.2k)
  - Combo products have >1 mode of actions
  - Primary Mode of Action= Provides the **most important therapeutic** action, expected to make the most contribution
Primary Mode of Action (example)

**Pad with Drug**
- Backing
- Film coated with adhesive
- Gel/Gauze pad with active ingredient
- Liner

**Adhesive with Drug**
- Backing
- Film coated with adhesive containing and active ingredient
- Liner

**PMOA = Wound dressing**
- Protects IV site or wound
- Absorb fluid
- Localized effect of drug
- 21 CFR 820 Quality System Regulation

**PMOA = Drug Delivery**
- Delivers drug dosage over time
- Pharmacological effect
- Systemic affect of drug
- 21 CFR 211 GMP
Factors affecting PMOA

- Proposed use of indication and use
- How product achieves its most therapeutic effect
- Relative contribution of each constituent to overall therapeutic effect
- Duration of the contribution from each component
- Scientific evidence supporting PMOA
FDA Combo Product with Drug PMOA

Drug and transdermal iontophoretic delivery system

Fluoride –Containing dental device for anticaries treatment

Antiseptic skin preparation swabs

http://www.fda.gov/CombinationProducts/JurisdictionalInformation/RFDJurisdictionalDecision/CapsularDescriptions“One-Liners”/ucm106666.htm
FDA Combo Product with Device PMOA

Drug Eluting Stent

Orthopedic Prosthesis coated with growth factor

Fluorescent imaging system for cardiac surgeries

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Development Timeline

Devices

- Concept or Feasibility
- Development
- Design Verification
- Design Validation
- Process Validation
- Commercial Transfer

Validation

- Phase I
- Phase II
- Phase III

Drugs or Biologics

- IND Review Phase

Combination Product

- NDA/BLA/PMA Filing
- MA Approval

Research
Agenda

- **Design Validation** and Process Validations
  - Usability and Human Factors studies
  - Difference between drug vs. device equipment validations
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- Challenges in compliance and Corporate Culture
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Design Validation

- Establishing by objective evidence that product specifications conform to user needs and intended use(s).
- Ensures product is designed correctly to achieve its intended purposes by conforming to defined user needs and intended uses and includes testing of production units under actual or simulated use conditions.
- May include clinical/nonclinical evaluations, including human factors testing, risk analyses, and software validation.
Design Validation

- Unlike medication dosages, combination products require user interaction (Human Factors).
- Safety profile and product efficacy/effectiveness depends on user interaction.
Design Validation (Summative)

- Gender
- Age
- Weight
- Medication(s)
- Use Conditions
- Native Language
- Lifestyle

Human Factors and Medical Devices ([http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HumanFactors/default.htm](http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HumanFactors/default.htm))
Design Validation

- Larger sample population (>100)
- Commercial production lots or ICH
- Final IFU / Package insert
- Final labeling / 2\textsuperscript{nd}/3\textsuperscript{rd} Packaging
- Usability Studies
- Final User or Application FMEA

Human Factors and Medical Devices
(http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HumanFactors/default.htm)
Inadequate product differentiation – Within a product line or across similar products

Unusual or unexpected device operation – E.g., needle stick injuries due to user holding device upside-down

Confusing or complex device controls

- Electronic display legibility or message clarity – E.g., font size and visual contrast – E.g., confusion from lack of clarity in IFU

Human Factors and Medical Devices (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HumanFactors/default.htm)
Human Factors: Transdermal

- Where to apply?
- How many patches to apply?
- How to apply?
- How long to wear?
- What to do during activities of daily living: showering, swimming, exercise?
- What to do if patch falls off?
- How to remove?
- How and where to dispose?

Human Factors and Medical Devices (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HumanFactors/default.htm)
Equipment Validations

- For Drugs (Pharmacopeia - US, JP, EU)
  - Analytical Equipment (Calibration, Syst.Suit, Analytical method val. Analytical instrument qualification) USP 1058 ICH Q2 (R1) or USP
  - Autoclave
  - Bioreactors

- For Devices (ISO, ICH, ASTM)
  - Lasers, gauges, Flow Meters (MSA: Gauge R&Rs)
  - Injection Molding, Electrochemical, etc
  - CMC, Manual Assembly, etc
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Process Validation (Drugs)

- Raw Materials
- Drug Substances
- Drug products
- Packaging
- Sterilization (Closure integrity)
- Distribution
- Serialization

Process Validation (Devices)

- Component qualification
- Process Characterization
- Mold qualification
- Assembly qualification
- Process Performance Qualification
- Sterilization

Risk Management Harmonization

- **ISO vs. ICH**
  - ISO 14971
  - ICH-Q9
  - FDA guidance

- **Alignment of risk policies and procedures**
  - Risk Policy on Combination Products (Includes ICHQ9 & ISO14971)
  - Stability, Strength, Quality, Purity, Identification (SSQuIP)
  - Form, Fit, Function or Performance
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Readiness for FDA Inspections

Drug / Device

21 CFR part 211

Biologics

21 CFR Part 820

Considerations

820.30. Design controls. 820.50 Purchasing controls.

21 CFR Part 600
Readiness for FDA Inspections

Who Regulates?

- In US the lead center is defined by the Primary Mode of Action (PMOA)
  - Center for Drug Evaluation and Research (CDER) \( \rightarrow \) NDA/BLA
  - Center for Devices and Radiological Health (CDRH) \( \rightarrow \) PMA
  - Center for Biologics Evaluation and Research (CBER) \( \rightarrow \) BLA

- Which Quality System prevails?
  - Drug or Biologics Good Manufacturing Practices (GMPs)
  - Device Quality System Regulation (QSR)
Challenges in Compliance

- Lack of experience with reviewing center (CDRH, CDER, or CBER) for MA filings
- Quality system lack policies, procedures, and resources to support combination products
- Misaligned systems or business processes
- Complacency with previous RA approval(s) on (legacy products) before 21CFR part 4
- Insufficient design validations
- Process validations performed separately or at non-production equivalent sites
Preventing FDA-483s or WLs

- Align policies and procedures to regulations and guidances (ICH, ISO, ANSI)
- Develop a robust business and development process
- Conduct proper design/purchasing controls
- Justify science and business decisions with risk based approach
- Educate teams, suppliers, and CMOs
Challenges in Corporate Culture

- Company may not realize they manufacture combination products.
- Organizational structure fosters work in silos.
- Resistance for change – Fear of the unknown
- Differences in development time or MA filings
- Lack of resources and/or the “right stuff”
- Unrealistic timelines or cumbersome processes
- Lack of leadership, vision, empowerment and decision making
In Summary

- Combo products provide many benefits
- New regulatory landscape and oversight
- Understand PMOA and FDA expectations
- Conduct proper design validation (Summative HF studies)
- Validate process in commercial line
- Embrace change management/culture
- Communicate Lessons Learned
Thank You