Combination Product Development: A Harmonized Roadmap For Efficiency, Compliance and Speed to Market

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Objectives & Agenda

• Current regulatory and development pathway (Device and Drug/Biologics)
• Key industry ‘lessons learned’ for combination products (CPs)
• Review a proposed integrated approach: the Sponsor and Contract Organization
• Final Thoughts & Best Practices
• Q & A
Primary Markets Served
- Pharmaceutical drug delivery devices
- Medical and diagnostic devices
- Medical and Surgical devices

Technology driven, global outsource design and manufacturing services
- 14 Global Manufacturing Locations; Four (4) Global Design Centers; and Four (4) Tool Build Centers.
- Full-range capabilities from design to manufacturing finished product
- Low-volume (smart assembly) through high-volume (high-speed automation)
- Annual revenue exceeds $600 million
- 3,400 people
Interesting Facts: Combination Product Regulatory Submissions

• From 2009-2014 there were 67 Requests for Designation (RFD) for formal combination product classifications and assignments

• Of those 67 RFDs, 69% were found to have been insufficient by the FDA, from the information provided by the sponsor

• Another 6% of the filings were withdrawn by the sponsor prior to the issuance of a decision

• ‘First to File’ does not always result in ‘right first time’ regulatory approval.
**Current Regulatory & Development Pathway**

**Medical Device**
Average cost to bring a new device (510K) to market is $34 Million (USD)

No guaranteed exclusivity or patent protection. Based on intellectual property (legal defense)

**Pharma/Biologic**
Average cost to bring a new drug product to market is $350 Million (USD)
New drug patent exclusivity = Avg. of 11.5 years

Average cost to bring an innovator biologic product to market – $1.2 Billion (USD)
Biologics patent / data exclusivity = 12 years
Current Regulatory & Development Pathway: Combination Products (CP)

CAUTION: Industry must learn the lessons from the traditional regulatory pathways and apply them accordingly to this new paradigm known as Combination Products.
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Key Lessons Learned From The Industry

Early – Late Stage Development Challenges

- Human factors/usability work is either incomplete or not provided
- **Limited or no human factors/usability work submitted prior to summative/HF validation testing**
- After or during submission: discovering new use-related problems at this point and “explaining them away”
- **Lack of effective follow up on residual risk and performance failures**
  - Residual risk and related hazards are not sufficiently identified with appropriate risk mitigation strategy
  - 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
- **Lack of or insufficient comparability testing regarding packaging changes**

Manufacturing Challenges

- **Conformance to both drug/biologic and device standards. QS needs to address both for combo product before, during and after use**
  - Lack of sufficient quality oversight for both sponsor and CMO
  - Lack of properly defined Master Supply or Quality Agreements for roles and responsibilities between Sponsor and CMO

Sterilization Challenges

- Consider the constituent parts and system as a whole. Challenges to resin properties vs. certain sterilization techniques such as EtO and eBeam
- **Choice for the lowest possible sterilization /lethality dose to achieve effective kill, yet not degrade the overall device / drug properties**
  - Package integrity post-sterilization
Key Lessons Learned From The Industry, (continued)

General Regulatory Challenges

- Applicability of appropriate regulations
- Determination of the PMOA (predicated on intended use)
- New regulations
- Rest of world countries that will have different approaches to CPs

FDA review center assigned by OCP does not = office performing PAI or registration

Each FDA review center has different set of laws, regulations and guidance. Each may differ in the amount of data required to support and successfully clear a submission approval

The acceptance of clinical trial data for FDA review based on (OUS)

- Risks of submission delay due to the lack of supporting data in the areas of clinical, toxicology; ADME/PK studies
- The impact of product and process changes both during and after submission
- Understanding how the product will be regulated globally
- Lack of Informally consulting with the FDA jurisdictional center and OCP to verify the anticipated review centers

Packaging Challenges

- Suitability of the Container – Closure System (CCS)
- Effects of different types of sterilization on both constituent parts and the system as a whole for stability purposes
- Packaging challenges for a sterile biologic along with an intricate device being kitted together
- Considering the packaging, handling, and distribution requirements for both constituent parts and the system as a whole

Protection from ambient and actual use environmental conditions
Up Front Integration In The Product Development Lifecycle Is Essential For:

- Speed To Market
- ‘Right First Time’ For Regulatory Submissions
Product Development: An Integrated Approach (Drug Delivery Device)

Product Development alignment with Quality Management System
- Stage Gate Formal Reviews (QMS)
- Phase Gate Technical Reviews (PDP)
- Manufacturing input and reviews built into the Product Development Process

PRODUCT DEVELOPMENT PROCESS

Charter S0  Proof of Concept S1  Development S2  Validation S3  Launch S4

- Program Initiation
- Strategic Planning
- Scaling & Scoping
- Design Research
- Concept Exploration
- Prototyping/POC Testing
- Sub-system Integration
- Refinement & Assessment
- Manufacturing Strategy
- Design Analysis
- Prototype Tooling
- Refinement & Assessment
- Design Verification Testing
- Scale-Up Planning
- Validated Manufacturing Environments & Processes
- Advanced Quality Planning
- Clinical / Market Entry

Successful Design Verification Test = Design Freeze
Product Development: An Integrated Approach

Drug/Biologic Development Considerations During So

- Development
- Early Stage Clinical
- Reimbursement
- Setting Global Regulatory Strategy & Expectations
- Strategy Integration (Cross Company Roles, Responsibilities, & Objectives)

Synergies Are Gained From Parallel Device / Drug Development Between The Sponsor and CMO

Drug Delivery Device Development

Design Development Process

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<th>Charter So</th>
<th>Proof of Concept S1 Phase 1, 2, &amp; 3</th>
<th>Development S2 Phase 4 &amp; 5</th>
<th>Validation S3</th>
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| • Program Initiation
  • Strategic Planning
  • Scaling & Scoping | Design Development | Validation | New Product Introduction |

Successful DVT = Design Freeze

PRODUCT DEVELOPMENT PROCESS
Product Development: An Integrated Approach

Synergies Are Gained From Parallel Device / Drug Development Between The Sponsor and CMO

Drug /Biologic Development Considerations During S0

Safety
- Toxicology
- Biocompatibility
- Biosafety

Clinical
- Design Study Mgmt.
- Design Appropriateness
- Clinical Endpoints vs. System
- Usability Engineering

Drug Delivery Device Development

Design Development Process

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- Sub-system Integration
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New Product Introduction
Product Development: An Integrated Approach

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Drug /Biologic Development Considerations During S0

**Safety**
- Toxicology
- Biocompatibility
- Biosafety

**Sterilization**
- Process Validation
- Material Appropriate
- System Interaction
- Drug-Device Interaction
- Sterility Testing Requirements

**Clinical**
- Design Study Mgmt.
- Design Appropriateness Clinical Endpoints vs. System Usability Engineering

**Package Integrity**
- Simulated Distribution
- Testing as a System
- Container Closure
- Seal Integrity
- Shelf Life / Expiration
- Package Validation
- Early Stage Clinical

**ADPROM**
- Co-Packaging
- Cross Labeling

**Stability**
- Constituent System stability Aging vs. Molecular Forced Degradation
- Drug-Device Interaction
- Impurity Profiles

Drug Delivery Device Development

**Design Development Process**

- Charter S0
- Proof of Concept S1
- Development S2
  - Phase 4 & 5
- New Product Introduction Validation S3
- Launch S4

Successful DVT = Design Freeze

- Design Development
- New Product Introduction

PRODUCT DEVELOPMENT PROCESS
Product Development: An Integrated Approach

Synergies Are Gained From Parallel Device / Drug Development Between The Sponsor and CMO

Drug /Biologic Development Considerations During S0

**Clinical**
- Design Study Mgmt.
- Design Appropriateness Clinical Endpoints vs. System Usability Engineering

**Validation**
- Scalable Process
- Rapid In-Process Testing
- Communication between Scientific and Engineering Disciplines

**cGXP – Commercial**
- Pharmacovigilance process
- ‘System” Risk Management
- Common QS Governance
- Gap Analysis for Regulatory Strategy
- UDI and IDMP Integration
- Change Control / Design Control
- Sample / Reserve Requirements
- Impurity Profiles

Drug Delivery Device Development

Design Development Process

- **Charter S0**
- **Proof of Concept S1** Phase 1, 2, & 3
- **Development S2** Phase 4 & 5
- **New Product Introduction Validation S3**
- **Launch S4**

Successful DVT = Design Freeze

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- New Product Introduction

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Product Development: An Integrated Approach

Synergies Are Gained From Parallel Device / Drug Development Between The Sponsor and CMO

Drug /Biologic Development Considerations During S0

Drug Delivery Device Development

Design Development Process

Charter S0

Proof of Concept S1 Phase 1, 2, & 3

Development S2 Phase 4 & 5

New Product Introduction

Validation S3

Launch S4

Successful DVT = Design Freeze

Design Development

New Product Introduction

PRODUCT DEVELOPMENT PROCESS

Drug Delivery Device Development

Drug /Biologic Development Considerations During S0

cGXP – Commercial
- Pharmacovigilance process
- ‘System’ Risk Management
- Common QS Governance
- UDI and IDMP Extension to Additional SKUs
- Change Control / Design Control
- Sample / Reserve Requirements
- Impurity Profiles (Lot – To – Lot Variation Analysis)
- Recall procedures and Cross-Notification
- Product / Process Capability (Control Plans)
- Operational Excellence (Process Optimization)
Final Thoughts: Best Practices To Apply Going Forward

• Treat the CP as both the sum of constituent parts, and as a ‘system.’

⭐ Establish clearly defined roles and responsibilities between sponsor functional areas (or) between the sponsor company and CMO.

• Early engagement by the sponsor, with the respective regulatory authorities is key to accurately establish the product profile, which feeds regulatory and marketing strategies.

⭐ Fully Define the regulatory strategy including (Reimbursement):
  - Centers for Medicare and Medicaid Coverage (CMS)
  - Other Global Government Cost Reimbursement Systems / Models

• Establish a fully integrated product development strategy between regulatory, R&D, Quality, and commercial functions.

• Engage well respected thought leaders in the industry that can act to augment and support key clinical strategies.

⭐ Establish a GXP ‘Phase Appropriate’ Quality System at all levels of the product development lifecycle.
Thank You!....... 

.....Questions ?

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Reference Materials


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6. Combination Products Coalition (CPC): Improving Patient Care through Better Combination Product Regulation Recommendations to FDA Centers from the Combination Products Coalition; May 2014.


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10 FDA, 21 CFR part 4, Current Good Manufacturing Practice Requirements for Combination Products, January 2015.

11 FDA, Frequently Asked Questions (FAQ) – Combination Products: Frequently Asked Questions About Combination Products, Updated May 2014.


14 ClinicalTrials.gov -- http://clinicaltrials.gov/
