Regulatory Considerations for Biologic/Device Products

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Joyce L. Frey-Vasconcells

Biological – Medical Device Combination Products

Examples of Regulated Biologic-Device Combination Products

- Metabolic support systems
  - Hepatic
  - Renal
  - Pancreatic
- Tissue repair/replacement
  - Cardiovascular
  - Cartilage and bone
  - Cornea
  - Muscle
  - Neurological
Combination Products

- Tissues
- Traditional Pharmaceuticals
- Traditional Devices

Developmental Challenges

- Complexity of products
  - Interactions between components
  - Involves different scientific discipline
  - Different regulatory requirements for each component

- Review process – regulations don’t always fit

- Communication –
  - Working with two different centers
  - Understanding the language

- Different reporting requirements
- Number of applications
- Development within company vs. working with another company
- Regulated differently in different countries
  - Introduce new terminology – tissue engineering

PROCESS CONTROLS

SOURCE CONTROLS

Assuring Safety/Efficacy

PRECLINICAL EVALUATION

CLINICAL STUDY - SAFETY and Efficacy
Product Characterization

Step-wise Approach to Application of Regulatory Requirements

Full characterization
21 CFR 610

Product Characterization

Pre-clinical

QA & QC, Clinical Monitoring Program

Prior to Phase I: need product safety testing and basic characterization info

Product Development Considerations

Product Characterization

Identity, purity, potency, viability, stability

Regulatory Concerns Common to All Cellular/Tissue Components

- Product Safety
  - Donor screening and testing
  - Adventitious agents, tumorigenicity, pyrogenicity
  - Biocompatibility testing with device

- Product Characterization
  - Identity, purity, potency, viability, stability
Regulatory Concerns Common to All Cellular Components

- Manufacturing Process – cGMPs
  - Control of product and process
  - Qualification of reagents
  - Segregation and tracking
    - different donors/different lots

- Reproducibility/Consistency of Product Lots
  - Development of in-process and lot release specifications
  - Ensure efficacy
    - Not dependent on autologous, allogeneic, or cell lines

Concerns Unique to Cellular Products

- Size of lot
  - one dose
  - one patient
- Timing of manufacture, testing, and administration
- Storage/holding/shipping

Questions: Ensuring a Safe, Pure, and Potent Product

- What should I test?
- When should I test?
- How should I test?
- All dependent on product and manufacture process
Device Considerations for Product Development

- Start with components already cleared/approved by FDA, if possible
- Pre-clinical testing should focus on modifications to already approved products
- Use well-established, “medical grade” materials (e.g., USP Class VI tested), if possible
- Consider the use of materials and components that adhere to recognized consensus standards
- Follow FDA guidance documents when possible
- Consult with FDA review staff early in the development process

REMINDER: Interdependence of Product Development Regulatory Concerns

Product Safety
- Donor Screening
- Product Testing
  - Microbial agents
  - Tumorgenicity
  - Pyrogenicity
- Biocompatibility

Characterization
- Identity
- Purity
- Potency
- Biocompatibility

Consistency
- Specifications
- Stability
- Comparability

Manufacturing
- Process control
- Qualification program
- QA/QC
- Tracking

Challenge for Combination Products

- Product transplanted may go thru additional remodeling
  - How control for environment of transplant site?
- May not be able to do complete release testing on final product
  - More emphasis on testing components up front
  - Combine with release testing = product consistency, safety, and characterization
- May need to make a surrogate along side of final product
  - Increase cost per unit
Preclinical Design Considerations

Goal of Preclinical Safety Evaluation
- Preclinical considerations for Phase I/II trials
  - Recommendation of initial safe dose & dose escalation scheme in humans
  - To determine an acceptable risk/benefit ratio in humans
  - Identification of potential target organ(s) of toxicity/activity
  - Identification of parameters to monitor clinically
  - Identification of inclusion/exclusion criteria
  - To discern the mechanism of action
  - Provide sufficient data to support labeling
  - Terminate potentially unsuccessful development programs

Selection of the Endpoint - Safety
- Attempt to incorporate the clinical application in the preclinical study design
  - Potential predictors of adverse effects in humans
  - Potential target organs
  - Clinical monitoring
  - Inclusion/exclusion criteria
- Correlation of PD profile w/ toxicity
Device Pre-clinical Testing

- Mechanical strength/integrity
- Biocompatibility
- Electrical safety
- Software validation/verification
- Shelf life
- Performance: in vitro (bench) and in vivo (animal models)
- Purity, potency and identity of cellular components

Take Home Messages - Preclinical

- The same amount of careful consideration in designing the clinical program should apply to the preclinical program
  - Talk with FDA early - prior to initiation of preclinical studies
- Utilize relevant animal species & animal models of disease in preclinical studies
  - No one species will be representative or predictive for all humans (including humans)
- A better understanding of fundamental & physiological mechanisms will help to provide a scientific basis for safer & faster clinical development

Clinical Trial Design Considerations
Clinical Efficacy Trial Design

- Size of Trial
  - Expected frequency and size of effect/benefit
  - Disease indication and stage of disease
    - Chronic disease vs. life-threatening
  - Patient Selection
  - Meaningful Endpoints
  - Potential Toxicity
    - Need to balance potential risk vs. potential benefits
  - Existing therapies
  - Safety database
    - Like products vs. novel

Summary - Clinical

- Ensuring safety is always FDA’s primary goal
- Good product development includes well-designed, well-executed, scientifically valid, interpretable clinical studies

Product and Clinical Development

- Preclinical
  - The first step in developing products for clinical use is to establish that they are reasonably safe to test in humans
- CMC
  - Establishing the safety, purity, potency, and consistency of a product
- Clinical
  - Data must be sufficient to assess risk-benefit and describe use in a label
- All must develop together and not independent!
Phases of Development

**Phase 1**
- First studies in humans – estimate maximum tolerated dose
- Initial determination of safety
- Spirit of GMP
- Product characteristics, assays, and process being defined

**Phase 2**
- Expanded safety studies
- Therapeutic exploratory – first look at efficacy
- Define – dose, schedule, route of administration
- Product assays being finalized

**Phase 3**
- Look at further safety issues
- Confirmatory trials for efficacy
- Evaluate risk-benefit relationship
- Provide adequate basis for labeling
- Product and process well defined
- Full GMP

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Must I do all 3 phases

- No, sometimes one can combine phases
  - Needs to be very carefully analyzed
  - Remember product must be ready also

- What you prove is what the label will say!!

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General Principles

- Novelty of the product
  - Components vs. product as a whole
- Extent previously studied
- Known or suspected risks
- Developmental phase
- Building process – never too early to start
One Size does NOT! Fit ALL
Flexibility Required

What is a Combination Product?
* Combinations of different types of products:
  * Drug-device
  * Device-biologic
  * Drug-biologic
  * Drug-device-biologic
  * NOT drug-drug, device-device or biologic-biologic
* They can be:
  * Physically or chemically combined
  * Co-packaged in a kit
  * Separate, cross-labeled products

Challenge

Primary Mode of Action
Consultation Regulations

Drugs
NDA/IND
COMP
AERS

Biologics
BLA/IND
AERS

Devices
PMA/510(k)/IDE
QSR
MCR
Office of Combination Products

- Mandated by the Medical Device User Fee and Modernization Act of 2002 (MDUFMA)
- Established December 24, 2002
- Organizationally within the Office of the Commissioner
- Work with industry and the three medical product Centers: CBER, CDER and CDRH
- Centers responsible for review and regulation
  - http://www.fda.gov/oc/combination

OCP Roles

- Make jurisdictional determinations
- Oversee/help coordinate premarket review
- Ensure consistent/appropriate postmarket regulation
- Develop policy, guidance and regulations
- Serve as resource for industry and review staff
- Resolve timeliness disputes

OCP Objectives

- Ensure combination product regulation is:
  - Clear
  - Consistent
  - Appropriate
  - Predictable
  - Transparent
Request for Designation

Request for Designation (RFD) – General Information

- Voluntary
- 21 CFR 3.7 has requirements – ≤ 15 pages
- For both combination and non-combination products
  - Classification and Assignment
  - Primary Mode of Action (for combination products)
  - Clarification of Regulatory Pathway
- 60 day clock
- Email: combination@fda.gov

When Should an RFD be Submitted?

- For any product where jurisdiction is unclear or in dispute.
- Before filing any application for premarket review (investigational or marketing application)
- Sufficient information to make a determination
Assignment for Combination Products -
Section 503(g) of the Act

* Lead Center based on its “primary mode of action”
* PMOA was not defined in the statute or regulations
* For some products, PMOA is difficult to identify
  * Early in development (just don’t know)
  * Products that have two (or more) completely different modes of action, neither of which is subordinate to other

Final Rule: August 25, 2005 Federal Register

* Definitions:
  * “Mode of action”
  * “Primary mode of action”
* Assignment algorithm:
  * Used when PMOA cannot be determined with reasonable certainty
  * Basis for sponsor’s assignment recommendation

Final PMOA Rule: Definitions

* MOA = means by which a product achieves its intended therapeutic effect or action.
  * Drug
  * Device
  * Biologic
* PMOA = single MOA of a combination product that provides the most important therapeutic action of the combination product.
  * Make the greatest contribution to the overall intended therapeutic effect
Algorithm for Combination Products

1. MOA
   - Drug
   - Device
   - Biologic
   - Device and Biologic

2. PMOA
   - Biologic
   - Device

3. Safety and Efficacy of similar product

4. Most expertise for significant safety and efficacy

Premarket Review

"timely and effective"

- Consultation
  - One center – regulatory responsibility and sign-off
  - One center – serves as consult to lead center

- Collaboration
  - Both centers have regulatory responsibility and sign-off

Additional Information

- Draft Good Manufacturing Practice Guidance
  - Published September 29, 2004

- Concept papers for comment
  - Adverse Event Reporting
  - Number of Marketing Applications

- Workshop - Cross Labeling
What must we do?

- Careful balance of potentially great but unproven benefits against uncertain risks
- Sensitivity to public concerns including safety and ethics
- Clear regulatory pathway
- Have the same path for like products
- Team approach for regulatory oversight and science
- Communications critical to success

Approach to Evaluating New Human Therapies

- Understand unique issues related to preclinical, clinical, manufacturing and characterization
- Encourage early interactions in order to facilitate an efficient review process.
- Regulation of biologic-device combination product will involve reviewers from both CBER and CDRH, regardless of which Center has jurisdiction.
- Flexible Regulatory Approach: Product Development is a Continuous Process from Pre-IND to Post-marketing. Elements of GLP, GMP, GCP need to be in place before Phase 1.

Recommendations

- One size doesn’t fit all combination products
- A combination product regulated as a device or biologic is not a traditional biologic or device
- Keep in mind the additive/modifying effect of the new constituent
- Understand the challenges and plan
- Consider full developmental scope (pre- and postmarket) throughout development
- Early discussions with both centers (and manufacturers, if applicable) at the table
- Contact OCP
Contact Information
Joyce L. Frey-Vasconcells
Executive Director, PharmaNet Consulting
PharmaNet, Inc.
815 Connecticut Avenue NW
Suite 800
Washington, DC 2006
Phone: 202-835-1345
Fax: 609-520-6953
Email: jfrey@pharmanet.com