CLARIFYING THE REGULATORY ROAD FOR COMBINATION PRODUCTS

Panelists: Kristin Neff  
Senior Director of Clinical Operations, TARIS Biomedical  

David Novotny  
Vice President, Medical Device & Diagnostics, Novella Clinical  

Cynthia Pritchard, PhD  
Senior Regulatory Specialist, Novella Clinical

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Moderator:  
Mark McCarty  
Washington Editor  
Medical Device Daily
ABOUT OUR EXPERTS

Mark McCarty, Washington Editor
*Medical Device Daily*

Mark has served as the Washington Editor for *Medical Device Daily* since March 2006. He has covered FDA’s regulation of the medical device industry from both a regulatory review and compliance / enforcement aspects, but has also reviewed Medicare reimbursement. Mark’s portfolio includes coverage of medical device advisory committees, congressional hearings and medical specialty society meetings. He has covered patent law and patent reform legislation, medical liability law, healthcare reform and the science of cardiovascular disease.

Kristin Neff, Senior Director of Clinical Operations, TARIS Biomedical

Kristin has spent the majority of her career at the intersection of project management and clinical operations in pharmaceutical, biotech and medical device organizations. Her most recent experiences have been leading clinical development/operations at smaller start-up companies including HeartWare, ConforMIS and most recently as the Senior Director of Clinical Operations at TARIS Biomedical. At TARIS, she is equally involved in strategic clinical development, oversight of clinical study operations and program management of the development programs.

David Novotny, Vice President, Medical Device & Diagnostics, Novella Clinical

David provides leadership, operational and strategic oversight for Novella’s medical device division, and has been involved in medical device and pharmaceutical research for over 13 years including overseeing US clinical operations for a medical device manufacturer specializing in wound care products and electrical delivery systems. His combination products experience includes strategic regulatory planning; management of feasibility through post-approval clinical trials for diabetes insulin pumps, implantable cardiac devices, drug eluting stents, surgical sealant compounds and various compounds for wound care closure indication.

Cynthia Pritchard, PhD, Senior Regulatory Specialist, Novella Clinical

Dr. Pritchard has over 30 years in the medical device/diagnostic/biologics industry, and has brought more than 30 Class II and Class III products from research into development through clinical trials and manufacturing to market launch. She has a strong Regulatory and Quality Assurance background, with extensive experience in FDA/ICH/ISO regulations, clinical project management, design control, and documentation, and has written over 30 successful submissions to CDRH and CBER divisions of the FDA and to European regulatory agencies.

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Combination Products – what matters in Clinical Operations

Kristin M. Neff
Senior Director of Clinical Operations
TARIS Biomedical, Inc.
Agenda (what you need to think about)

- Drug or a device?
- Challenges of “blinding” a combination product
- How important is training?
- Combination Product safety events
- Investigational Product events
My experience with combination products

- Combo products regulated as devices
  - Drug eluting ureteral stent
  - Drug coated cardiac stent
- Combo product regulated as a drug
  - Lidocaine releasing intravesical system
- And lots of devices...
  - Custom knee replacements
  - Left ventricular assist device
  - Pelvic floor sling
Does it matter? **YES and NO**

For the most part... NO

- FDA expectations are becoming more and more aligned for drug products and devices
- Clinical Study execution and compliance to regulations are equally rigorous
- However...whether the combination product is regulated as a drug or device - it is usually the “device“ that requires the most attention
How do you blind a combination product?

- Not easily...

- Very difficult to make two products that are not the same look/feel/behave the same
How do you blind Investigator/site staff?

Not easily...

› Must follow precise and well defined packaging/labeling blinding procedures
› Ensure placebo and active products are indistinguishable to the naked eye
› Ensure placebo and active products look, feel and behave the same

What if the placebo device is not actually a placebo?
› May need to include a “sham” procedure
Challenges of a Sham Procedure

- Can only be single blind
- Requires adequate “acting” on the part of the Investigator/site staff
- May result in extra activities that appear to be “no value added”
- May be additional risk associated with the procedure
Very important!
The effectiveness of a combo product is directly related to the skill of the individual placing the product
Need to have a study specific/product specific training plan
Need to have qualified trainers
There is a learning curve - may need to consider a “training” period before clinical study data is collected
Investigator Training - How/Who/When

- **How?**
  - Face to face
  - Hands on – watch one, do one, teach one
  - Webinar

- **Who?**
  - Investigator
  - Sub-Investigators – depends on their role
  - Study coordinators
  - “Unblinded” site staff

- **When?**
  - Before study begins
  - What if study delayed?
  - What if trained Investigator hasn’t placed product in a long (define long?) time?
  - Do you need to retrain Investigators for a new study with same product?
Safety Events – things to consider

- Need to determine how to assess causality related to a drug/device combination product
  - Causality due to drug component?
  - Causality due to device component?
  - Causality to combination product as whole
  - Need to check data consistency

versus
Safety Events – things to consider

- What about a procedure to place a device?
- Need to consider if and how the procedure effects safety events
  - Investigational ureteral stent versus approved ureteral stent
  - Investigational drug/device product versus standard of care if standard of care does not require a procedure
  - Investigational drug/device product versus sham procedure
Investigational Product Events

- Any observation of the Investigational Product not behaving as intended

Examples

- Investigational Product does not appear as intended at the time of removal from the packaging
- Drug eluting ureteral stent - unintended voiding of the Investigational Product
- Drug coated cardiac stent – cardiac stent becomes occluded
- Investigational Product is damaged in any way during insertion or removal procedures
An Investigational Product Event could occur any time between when the Investigational product is removed from the packaging through the insertion/removal procedures and/or lifetime of the product.

Helpful to have a trigger for sites to alert sponsor of IPE – time sensitive analysis!
Investigational Product Events

- Is IPE associated with a safety event? ⇒ needs to be assessed by the Investigator

- IPE follow-up
  - Investigation
  - CAPA
  - Notification to sites
Clinical Operations - Take home message

- Every investigational product and every clinical study will be unique and have unique challenges
- **Pay close attention** to the device component of the drug device product
  - Blinding
  - Training
  - Safety events
  - Product events
- Learn from past experiences
Happy trials!

Happy Trails

Thank you
Medical Combination Product
U.S. Regulatory Challenges

Cynthia Pritchard, PhD
Senior Regulatory Specialist, Novella Clinical
Combination Products

- Descriptions
- Challenges
- Steps
- Pitfalls
- Recommendations
Description

► Therapeutic and diagnostic products
► Mix of ‘regulated components’
  ▪ Device
  ▪ Drug
  ▪ Biologic
Description

Two or more regulated components:

- Physically / chemically combined; single entity
- Packaged as unit
  - Packaged separately but...Intended for use only with another specific component
  - Both required to achieve intended use
Challenges

Components may be normally regulated by different regulatory authorities

- FDA
- EPA
- CDC
Challenges

- Blur historical separation between FDA Centers
  - CDRH – devices
  - CBER – biologics
  - CDER - drugs
Challenges

► Raise regulatory, policy, and review management issues

► Difference in regulatory pathway for each component impacts entire process
  - Development
  - Clinical
  - Manufacturing
  - Submission
  - Post-market
RFD Process Steps

Request for Designation is **required**

- Request *informal* designation from FDA
- Company may make designation
RFD Process Steps

► Formal Designation
  ■ Company
    • Writes
    • Submits
  ■ FDA
    • Notifies
    • Reviews
    • Assigns
    • Designates
Potential Pitfalls

► Mode of Action

► Intended Use
Potential Pitfalls

Mode of Action

- Describe all known MOA
- Each component has at least one MOA
Potential Pitfalls: Mode of Action

Therapeutic = any product effect or action to:

- Diagnose disease
- Cure, mitigate, treat or prevent disease
- Affect body structure or function
Potential Pitfalls: Mode of Action

Each part as an MOA:

- Device – mechanical
- Drug – chemical or immunologic
- Biologic – vaccine, blood component or derivative
Potential Pitfalls: Mode of Action

1) Describe all MOA

2) Pick Primary Mode of Action (PMOA)
   - One only
   - Greatest contribution of intended effect

3) Define rationale
Potential Pitfalls: Mode of Action

► Correct definition of PMOA is key
► Assignment to ‘Lead Center’ based on PMOA
Pitfall: Intended Use

Example: Device + Antimicrobial

Potential Claims

1) Inhibit bacterial contamination of device
2) Inactivate microorganisms on patient
3) Reduce infection rate
Pitfall: Intended Use

► Claim 1: Inhibit bacteria on device
► Example: surgical drape w/agent to maintain sterile field
  ■ Designation: PMOA = device
  ■ Lead Center: CDRH
  ■ Testing: preclinical
Pitfall: Intended Use

► Claim 2: Inactivate microorganisms on patient

► Example: surgical drape w/ agent to maintain sterile field
  ■ Drape serves a barrier function, but…
  ■ New claim >> ‘risk’
Pitfall: Intended Use

Claim 2: Inactivate microorganisms on patient
- Designation: device
- Lead Center: CHRH
- Testing: safety and efficacy studies
Pitfall: Intended Use

Testing: safety and efficacy studies

- If new antimicrobial agent
  - Biocompatibility
  - Animal testing
  - Bioavailability/bioequivalence

- Lead Center: CDRH, CDER involved

- Path: IDE > clinical studies > submission
Potential Pitfalls: Intended Use

- Claim 3: Reduce infection rate
- Example: surgical drape w/ agent to maintain sterile field
- Same designation but ...
- Add extensive and long-term clinical studies
Recommendations

Before:

- Obtain regulatory assessment for proposed product
- Explore ‘staged’ pathway
- Do not ask for designation too early
Recommendations

During

- Include all elements
- Follow exact order

Key:
- Wording
- Detail
- Choice of predicates
- Knowledge of previous FDA decisions

- Respond quickly to FDA emails
- Send formal response letter
Recommendations

► After

■ Favorable

■ Unfavorable
  • 15 days
  • New info only
  • Addendum/new cover letter

■ Designation
  • Binding
  • Change
Thank you!
Medical Combination Product
Clinical Trial Execution

David Novotny
Vice President, Medical Device & Diagnostics
Novella Clinical
Considerations

► When to engage your CRO of Choice
  ■ How do CROs add value in early and late development stage
  ■ Request for Information (RFI) process

► Clinical Operations Core Competencies
  ■ Regulatory and Clinical Operations
  ■ Therapeutic + delivery focus
  ■ Pre-Clinical Operations (e.g., core lab)
  ■ Safety Reporting Considerations
  ■ Costing models for pilot, pivotal, post-market
  ■ Feasibility and Site Selection
What should your CRO look like?

Pre-Clinical
- Regulatory Assessments (U.S. and Europe)
- Device Classification/Predicate
- Device Searches & Strategy
- Creation of Technical Design Files
- Literature review
- Protocol review and/or guidance during development
- CE Mark Planning
- FDA Clearance Planning
- Auditing
- Registered Agent Services
- SOP development
- Class II 510(k) Meeting Request and Submission Dossiers
- Pre-IDE/IND/BLA Meeting Participation
- Report of Prior Investigations
- Class III PMA Support
- IDE/IND Regulatory Support and Submissions

Clinical
- Program Management
- eCRF Design & Programming
- EDC Application Hosting (Oracle’s InForm™)
- Study Start-Up & Investigator Recruitment
- eClinical Investigator & Staff Training
- Clinical Monitoring
- Data Management
- Biostatistics
- Medical Writing
- Medical Monitoring
- Device/Drug Safety
- Agency Audit Support and Warning Letter Resolution
- Health Economic Licensing and Analysis

Post-Approval
- Medical Writing
- Publication Support
- CE Pre-approval Support
- CER Gap Analysis
- Program Management
- Registry, Outcome, Retrospective
Defined lines between drugs, devices, biologics
Drugs, Devices, Biologics = Combination Product

- Terminology
- Classifications
- Differences and Similarities
- Clinical Study Considerations
  - Evidence generations strategies
  - Safety/Efficacy endpoints
  - Health Related QoL
  - Standard of Care
  - Safety nuances
Drug/Device Comparison Chart

Submissions and Regulations

- FORM 1571 IND → IDE Check List
- FORM 1572 SOI → Investigator Agreement
- 21CFR 312 IND → 21 CFR 812 IDE
- 21CFR 314 NDA → 21 CFR 814 PMA
- 21CFR 316 Orphan Drug → 21CFR 814 HUD/HDE
Drug/Device Comparison Chart

Quality Systems/Manufacturing Controls

21 CFR 210/211 CGMPs → 21 CFR 820 QSR
ISO 9001 & CMCs → ISO 9001/13485
Drug Master File → Device Master Record
Design History Record
21 CFR 201 Labeling → 21 CFR 801 Labeling
21 CFR 812 Labeling

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Pre-Clinical Services

► Regulatory determination and guidance
  ■ IDE, IND, BLA, HDE
  ■ Ex. Labeling, Instructions for Use

► CAB development and management
  ■ Strategic direction, trial design, endpoints, publication

► Protocol/ Dossier Development
  ■ Sample size determination
  ■ S/E Endpoints
  ■ Intended Use and PMOA
  ■ Monitoring
Clinical Services

► Study Execution

■ Site Feasibility and Selection
  • Investigator database, enrollment metrics, quality

■ Clinical Management
  • Training on device/drug delivery, storage conditions

■ Data Management
  • Form creation; SAE, Malfunction/Failure
  • Database build

■ Medical Writing
  • Annual Reports and CSR

■ Safety Management
  • Branch specific reporting CDER/CDRH
  • Cross reporting

■ Quality Assurance

■ Product accountability
  • Drug, Device, Biologic expiry
  • Performance updates
Costing and Budget Models

► Building a competitive, accurate budget reflecting scope of work

- Insourcing vs. Outsourcing
- Milestone vs. Units
- Change Order metrics
- Cost Drivers
  - Clinical Monitoring
  - Safety
  - Data Management

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Closing

► When to engage your CRO of Choice

■ Early stage through late stage
  • Continuity

■ Choose full service partner that can support lifecycle of your product

■ Regulatory Experience
  • FDA; CDRH, CDER, CBER

■ Therapeutically and product aligned

■ Global scalability

■ Experienced staff
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Or

• If you have called-in on the telephone, press *1 on your touchtone phone.
• If you are using a speaker phone, please lift the receiver and then press *1.
• If you would like to withdraw your question, press *1.