Drug-Device Combination Products

Topic Overview

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Definition: Drug-device combination product

- **“Single entity”** or **“integral”** product is comprising two or more different regulated components (drug/device/biologic) that are physically, chemically, or otherwise combined or mixed;
- **“Copackaged”** or **“kitted”** unit in a single package comprising drug and device, device and biologic, or biologic and drug products;
- **“Cross-labeled”** drug, device, or biologic product packaged separately that according to its investigational plan or proposed labeling is intended for use only with another individually specified drug, device, or biologic product where both are required to achieve the intended use, indication, or effect.
Topics for discussion

1. Human factors studies
2. Lifecycle management / product changes post-approval
3. Design control requirements
   a) clinical trial phases
   b) legacy products (retrospective analysis)
   c) “simple” class 1 co-packaged devices (commercially available kit contents)
Human factors studies

- Human factors studies are “part of the process to maximize the likelihood that the combination product user interface is safe and effective for use” (quote from new FDA draft guidance – see notes section)

- Design validation includes:
  - risk analysis which identifies/analyzes potential use-related hazards
  - evidence generation that demonstrate the combination product user interface can be used by intended users in the expected use conditions for the intended use ... all “without serious use errors or problems”

- Formative studies are iterative during development that inform:
  - the need for design changes (product, package, label)
  - content of the HF validation study

- HF validation study assesses the ability of the user to successfully and safely perform essential/critical tasks
Industry Challenges

• Determining appropriate HF validation study design, eg, defining critical tasks, training and learning decay.

• Adequate formative studies to comprehensively inform the design, risk mitigation.

• Design Validation - complete HF summative study before Phase 3?

• Incorporate learnings from Phase 3 and beyond-revalidate?
More Challenges

• “Use” of the to-be-marketed product in clinical trials - investigational device requirements preclude using final label.

• CDER reviews validated IFU – what changes require revalidation?

• Potential conflict between CDER/CBER/CDRH with interpretation of HF studies and mandated changes.
Lifecycle Management

- Guidance: “Submissions for Postapproval Modifications to a Combination Product Approved Under a BLA, NDA, or PMA” (2013)
- Need a postmarket submission for the combo if a change:
  - is made to any constituent part that would have required a postmarket submission if the constituent part were a standalone product
  - to any of the constituent parts would otherwise trigger the requirements associated with the application type used for approval of the combination product
- Submission type follows the rules for the application type used for the original approval of the combination product
Lifecycle Management (Drug PMOA products)

- Use NDA/BLA/ANDA submission types – PAS, CBE-30, CBE, AR

- Can apply definitions in drug regulations at 21 CFR 314.70 to changes in device constituent part
  - “potential to have an adverse effect on the identity, strength, quality, purity, or potency ... as these factors may relate to the safety or effectiveness of the drug product”

- Some changes may already be addressed in guidance “Postapproval Changes to NDA/BLAs” (changes in elements of container closure systems that are also device constituent parts)
Future of Lifecycle Management

• For drug products in CDER and CBER, FDA has published draft guidance on “Established Conditions”(2015)
  – Explains that postapproval changes to “established conditions” must be reported; changes to other aspects of the product or process can be managed under the pharmaceutical quality system without the need for a submission
  – Concepts are being incorporated and expanded upon in ICH Q12 “Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management”

• At this stage, unclear whether Established Conditions/Q12 will be applied to drug PMOA combo products or to drug constituent part of device PMOA combo products
Challenges

- Combination product guidance only addresses parallels between NDA/BLA and PMA; does not address device constituent part that would be regulated under 510(k)
- What about device constituent parts expected to iterate often (e.g., software)
  - One approach for products regulated under NDA/BLA (prior to implementation of Established Conditions) is use of Comparability Protocols to gain agreement on submission type and content for anticipated changes (see draft guidance “Comparability Protocols for Human Drugs and Biologics: Chemistry, Manufacturing, and Controls Information”)
Design Control Requirements

Design controls are required for combination products under 21 CFR Part 4

Three areas of design control application for discussion:

• Clinical trial phases
• Legacy products (retrospective application)
• “Simple” class 1 co-packaged devices (commercially available)
Clinical Trial Phases

• Investigational combination products are exempt from 21 CFR Part 820 except for design control requirements
  ▪ Design controls considered “initiated” when formal management commitment has been given to a project entering development (i.e., design and development plan is approved or when design inputs are approved for implementation)
  ▪ Feasibility and early clinical phase activities may occur prior to the establishment of formal design control for a combination product; apply appropriate level of controls, leveraging GxPs (e.g., GCP, GLP, GMP)

• For clinical studies, the manufacturer needs to consider:
  ▪ Intended use and functional/performance requirements needed for success of study endpoints and to ensure study subject safety (positive benefit risk profile)
  ▪ Type and amount of design verification and validation data that is appropriate to the phase of development; requirements for feasibility, Phase 1 and 2 clinical studies will likely differ than those for Phase 3 clinical studies
Legacy Products (Retrospective Application of Design Controls)

- CGMP Final Rule Preamble: Agency will provide guidance on how to comply “including with respect to coming into compliance with pre-manufacturing design control requirements for products currently being marketed” (aka legacy products)

- DRAFT FDA Guidance: “Appropriate to leverage existing data in developing a design history file for a combination product that may not have been developed under design controls”
  - Examples: existing specifications may become part of the design output documentation; testing performed prior to distribution may be included as design verification and validation documentation
  - Manufacturer is responsible for assembling available information and assessing what, if any, additional information and evidence may be needed to support
  - Do not need to prepare a development plan or conduct design review meetings for currently marketed combination product
“Simple” Class 1 Co-packaged Devices (commercially available)

• CGMP Final Rule Preamble: Kit that includes two or more types of medical products (eg, a device and a drug) is a co-packaged combination product; the manufacturer of the kit is subject to Part 4 requirements
  ▪ Class 1 devices exempt from the QS regulation except record keeping and complaint file requirements (21 CFR 820.180/820.198)
  ▪ If “Convenience Kit” then no additional CGMP requirements would apply to the constituent parts; only demonstrate compliance with CGMP requirements with respect to kitting manufacturing activities

• If finished device is purchased, the combination product manufacturer is not required to retrospectively “design” the part
  ▪ Understand the part’s existing design specifications in order to perform design controls properly for its use in the combination product
  ▪ Comply with design control requirements for any modifications that need to be made to the part for use in the combination product
CMC Focus Group Face-to-Face Meeting
May 4, 2016 | Bristol-Myers Squibb Company • Plainsboro Township, N.J.

Slides for Breakout Sessions
Hypothetical HF Example: Autoinjector

- Series of 3 formative HF studies each result in IFU modifications
- Summative study successful (low residual risk, conducted in parallel with phase 3 clinical studies)
- BLA review: FDA recommends/requires font change so IFU must be reformatted
- Revalidate with new HF study?
Hypothetical HF Example: change to actuator for an approved metered dose inhaler

- Design controls?
- HF studies?
- Clinical comparability (PK) studies?
- Submission type?
Design Controls - Clinical Trial Phases

- Hypothetical Examples for Discussion
  - Drug in a Phase 1 clinical study co-packaged with and administered by a marketed (commercially available) syringe
  - Combination product in a Phase 3 study where the device constituent part is a Class I device not subject to design controls
  - Combination product in an early feasibility or Phase 0 study where:
    - Clinical study endpoints are for basic physiological research
    - Manufacturer does not intend to develop the device for commercial distribution
    - Data from the study will not be used to support marketing applications

- What differences may exist between design verification data applicable to an early feasibility/Phase 0 clinical study vs. a Phase 3 study? What about a bioequivalence study conducted by healthcare provider vs. a home use study?
- What GCPs allow for more manufacturer control than when a product is in commercial distribution?
- Why is it important to have appropriate controls in place for the design of a combination product used in any clinical study?
Legacy Products (Retrospective Application of Design Controls)

- Hypothetical Examples for Discussion
  - Prefilled Syringe (single entity combination product)
  - Drug delivery kit that includes a vial, vial adapter, diluent syringe, needle (co-packaged combination product)
    - Establish Part 4 compliant Quality Management System (future changes)
    - Leverage CAPA system for planning, implementation, effectiveness checks
    - Document design input and output requirements
    - Generate risk management documentation
    - Assess available evidence to verify and validate design
    - Based on risk analysis/health hazard assessment, determine if prospective data is needed to assure safety and effectiveness
    - Establish design history file (DHF) for the combination product

- What does it mean to apply a ‘risk-based approach’ to retrospective DHF construction?
- How much evidence is ‘enough’ to validate the design?
“Simple” Class 1 Co-packaged Devices (commercially available)

- Design controls ... do they apply to the kitting manufacturing activities?
  - Design control requirements apply to the combination product as a whole
  - Co-packaged combination products, including CGMP activities associated with ‘kitting’ convenience kits, have design inputs and outputs which are established through design verification and validation activities (plus design and development planning, design reviews, design transfer, control of design changes, and a design history file)
Summary / Wrap-up on Drug-device combination products
Design Control (DC) Requirements

– Range of expectations depending on device complexity; thus SOPs may reflect the need for some flexibility
– DC complexity varies per phase of clinical development
– Combination product DC is needed even when including a commercially marketed device
  • If device is exempt from DC, apply DC to combination product
– Consider possible hazards related to device functionality, mapping to CQAs, which could later appear in a patient complaint and address it in DC. Develop a proactive script when receiving complaints to gather enough details.
Design Control Requirements, cont.

– Device platform (same device with different drugs):
  • Possibly leverage data across products for the same population/environment of use (may have slight modifications; need to ‘make the case’ in the narrative)
  • Applicability of platform data depends on populations and environments of use

– Stability formal studies required together or separate?
   Address both the constituent part and the combination product (include the drug-device interactions)
Human Factors (HF) studies

- The Human factors *process* is important.
- Important to have formative studies to assess ranges of design options, driving towards commercialization.
- Important to evaluate in simulated conditions that represent actual use.
- HF guidance intent is not to signify that an HF study is a clinical trial.
- From an HF perspective, DMEPA generally expects that simulated use studies should be sufficient.
- If the combination product will be used in a pivotal trial, need to discuss with the Clinical review division early.
A lot of recent improvement but confusion still exists for:

– Training: when to include training in a protocol
– User Groups that should be tested (e.g., use of surrogate populations)
– HF studies are qualitative
– If unsure as to why the Agency is requesting labeling changes, Sponsor needs to ask (suggest that the Project Manager ask the appropriate reviewer)
Human Factors studies, cont.

– Understand the user needs and similar products in the space that may lead to negative transfer
– Caution: over-reliance on labeling/instructions
– Document the rationale behind the risk mitigation strategies (including the IFU development).
Lifecycle Management
– Comparability protocols
  • Use them for **anticipated** changes to either constituent part
  • To be in one protocol, changes need to be related
  • Caution on threshold of cumulative changes if multiple protocols and/or changes
  • Possible usage of a comparability protocol to manage iterative (frequent) changes like software – avoid submitting each software update as a PAS!
Lifecycle Management, cont.

– Will still have residual risk after validation; complaint information received during LCM may provide additional information on occurrence and severity of risks that were thought to have been appropriately mitigated

– Design Controls requires a procedure for changes to be evaluated via risk assessment / change mgmt., even during development

– When is a clinical comparability study needed to support change to a “similar” device? Topic for future work...