CMC Considerations for Combination Products

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**Co-Speakers/Moderators:** Ashley Boam (FDA); Scott Furness (FDA); Jason Lipman (Janssen R&D, LLC); Stefan Leiner (Boehringer-Ingelheim)

Speaker comments and provided slides are not intended to represent the official views of the speakers' organizations or AAPS
What is a “combination product”* ???

**US FDA**
A medical product comprised of a “combination” of a drug and/or device and/or biologic (any two or all three) and are “marketed together.” (21 CFR 3.2)
- **“Single-entity”** or “integral” (e.g., prefilled syringe/injector; MDI)
- **“Co-packaged”** or “kitted” (e.g., Vial with syringe and needles)
- **“Cross-labeled”** (e.g., specific 510(k)’d device intended for branded drug)

**EU EMA/EC**
- Only “Medicinal Products” (Drugs, Biologics, ATMPs) or “Medical Devices” - CE Marked.
- Integral drug-device combinations (e.g., prefilled pens, MDIs) are also “Borderline Products” (MDD MEDDEV 2.1/3) regulated as medicinal products. Follows the MPD plus conformance to the Annex I Essential Requirements of the Medical Device Directive

**Other Markets**
Drug-Device combination products generally assigned as drug/biologic product or a medical device; Few formal regulations – requirements negotiated; Some markets (Canada) have clearer guidances

* Fixed-combination (drug-drug) prescription drugs (also combination products) are regulated as drugs (21CFR 300.50)
What are the new FDA cGMP rules that apply to single-entity and co-packaged combination products?

§ 4.4 (a) . . . compliance shall be achieved … a CGMP Operating System that is demonstrated to comply with:

- (1) the specifics of each set of CGMP regulations…

- § 820.20. Management responsibility.
- § 820.30. Design controls.
- § 820.50. Purchasing controls.
- § 820.100. Corrective and preventive action.

- § 211.84. Testing and approval or rejection of components, drug product containers, and closures.
- § 211.103. Calculation of yield.
- § 211.132. Tamper-evident packaging requirements for over-the-counter (OTC) human drug products.
- § 211.137. Expiration dating.
- § 211.165. Testing and release for distribution.
- § 211.166. Stability testing.
- § 211.167. Special testing requirements.
- § 211.170. Reserve samples.
How do design controls drive combination product development?

Expected approach to development and setting release/stability specifications – 21 CFR 820.30/ ISO 13485

- **Design and Development Planning** (Device/Combination Product Development Plan)

- **Design Inputs** (What does the user/patient require of the device? What technical and “suitability” characteristics are required of the device? **How do you consider design inputs related to a biopharmaceutical?**)

- **Design Outputs** (design phase - performance acceptance criteria, specifications, drawings) May be used to specify off-the-shelf products. **Biopharmaceutical specification is also a Design Output**

- **Design Verification** [bench performance tests to confirm specifications (Outputs) are met] Confirmation that the specific device(s) are **suitable with a specific biopharmaceutical**.

- **Design Validation** [Establishing by objective evidence that the device(s) meets user needs and intended uses (Design Inputs); user/clinical/human factors studies with testing of the IFU, process validation, functional stability] Tested with the target population (and for/with **biopharmaceutical**, where necessary).

- **Design Changes**: document/approve design changes and reasons during development.
Device development should also conform to ICH, ISO and FDA Guidances

- **ICH M4Q - Container Closure** — “The suitability of the container closure… “reproducibility of the dose delivery from the device when presented as part of the drug product.” (32P24 and 32P7)
- **ICH Q6A Specifications**: Test Procedures and Acceptance Criteria: “…parenteral formulations packaged in pre-filled syringes, autoinjector cartridges, or the equivalent should have test procedures and acceptance criteria related to the functionality of the delivery system.” (32P5)
- **ICH Q1A (R2) Stability Testing**: including “functionality tests (e.g., for a dose delivery system)” (32P8)
- **ICH Q8(R2) Pharmaceutical Development**:
  - “Critical Quality Attributes (CQA) (3.2.P.2.2): For other delivery systems …, such as aerodynamic properties for inhaled products, …, and adhesion properties for transdermal patches.”
  - “Drug Product Container Closure System (3.2.P.2.4): If a dosing device is used (e.g., dropper pipette, pen injection device, dry powder inhaler; demonstrate that a reproducible and accurate dose is delivered under testing conditions that, as far as possible, simulate the use of the product.”
- **ISO Standards: Particular requirements**
  - ISO 14971:2007, Medical devices — Application of risk management to medical devices
  - ISO 20072:2009, Aerosol drug delivery device design verification — Requirements and test methods
  - ISO 11608 2012) – Series on injection systems
- **FDA Guidances**:
Discussion Topics

- Practical implementation of device Design Controls in pharmaceutical product development for new and legacy drug products
- Design Validation through Human Factors Studies (HFS) per CDRH guidance and/or "use" of the to-be-marketed product in clinical trials
- Developing and justifying reportable delivery device specifications in a "Pharma world."
- A device company wants to combine your drug with their device. How can you help them with Pharma requirements?
Breakout session overview

- For each breakout, we will poll the audience and lead discussions based on topic familiarity.
- For each topic, we will pose a hypothetical scenario and discuss related challenges and potential solutions.
  - **Industry challenges**
    - Identifying/understanding regulatory requirements and guidances
    - Reconciling the absence of a least burdensome approach for combination product (drug) development
    - Balancing regulatory risk
    - Developing regulatory strategies (i.e., starting with User Requirements)
    - Proving equivalence or stand alone safety and effectiveness
  - **FDA challenges**
    - Determining appropriate level of evidence / requirements for approval
    - Collaborating with large review teams with potentially divergent views
  - **Intended to facilitate sharing of experience - Not a Q and A for the Agency**
Practical implementation of device Design Controls

- **Case Study:** PharmCo has been marketing a liquid oral drug kitted with a “Liquid Medication Dispenser” [Class I device; 880.6430; (oral syringe, dropper, cup, spoon)] exempt from Design Controls.*

- **Discussion Questions:** What actions are appropriate?
  - Assume that the exemption continues to apply to Class I exempt devices under the Combo cGMP rule?
  - Write and implement PharmCo SOPs for the 820 requirements?
  - Re-label the dose accuracy test report as “Design Verification”?
  - Prepare a Design History File retrospectively mapping development activities to respective elements of Design Controls?
  - Conduct gap analysis and conduct additional new verification and validation (e.g., HFS) activities?
  - This is an OTC drug product – Does it matter?

* Very similar legacy product issues arise with Metered Dose Inhalers and PFS glass barrels (which have no CFR device regulatory status) and Design Control gaps – can be included in the discussion.
Design Validation: Human Factors Studies or Clinical Trials

Case Study: In an IND Type C meeting, PharmCo was asked by CDER to conduct formal Human Factors Studies (HFS) of a prefilled injector per FDA guidance and to study “patient handling” for usability in a clinical trial.

Discussion Questions:

- What development plans are appropriate?
  - Conduct HFS as the pivotal data; record/investigate device complaints including use errors in the trial?
  - Conduct HFS plus Phase 3 usability substudy (~100 subjects)?
  - Conduct PK study with self-administration – no HFS study?

- Task deviations were seen in the HFS. How do you choose between design changes or IFU changes, or accept as a residual risk?

- The IFU was validated in the HFS but late BLA/NDA reviewers suggested significant IFU changes. What is the path forward?

- What is required for Post-P3-Study or postapproval device changes (cosmetic or minor functional)?
Developing and justifying delivery device specifications

➢ Case Study: A delivery device “actuation button” force specification needs to be established among other technical specifications – some of which may be release specifications.

• Discussion Questions
  – At what point in development should the button force specification be set?
    • As a Design Input via formative HFS which is then validated?
    • As a specification derived from process validation batches and lots used in the clinical studies?
  – How are release specifications determined?
    • Limited key tests that assure overall quality?
    • Extensive testing of all design specifications?
  – How are specifications derived from “reasonable engineering judgment” (e.g., delivery time) justified (e.g., in eCDT 32P56)?
Supporting device development with your drug product

**Case Study:** PharmCo has a joint venture with DeviceCo to develop an antimicrobial coating for DeviceCo’s implant. PharmCo needs to advise DeviceCo how to comply with the relevant Combo cGMPs in the implant’s development.

**Discussion Questions:** What does PharmCo advise for:
- Process Validation conforming to both drug and device regulatory expectations?
- Container closure testing/acceptance requirements?
- Calculation of yield?
- Stability studies for the drug applied to the device?
- Sterility and pyrogenicity testing of released lots?
- Finished product sample retention?
Back-up Slides
For Breakout Sessions Only

Alternate scenarios, additional inputs to the current scenarios, and additional potential questions
Wrap Up Slides: CMC Considerations for Combination Products – Workshop
Summary of Breakout Sessions

The comments and views presented here are those compiled from the audience and are not necessarily representative of the moderators or their organizations

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Discussion Topics

- Practical implementation of device Design Controls in pharmaceutical product development for new and legacy drug products
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Practical implementation of device Design Controls

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- **Breakout discussions/ concerns:**
  - Design controls are required for the combination product even if it is a class I device
    - New SOPs are necessary
  - Consult with OCP to create design inputs (user requirements) and potentially design validations per FDA expectations
  - Design controls imply risk-based development process with a combination product perspective including patient needs – these should be appropriate for the legacy product
  - For legacy products, existing testing can be mapped to design control elements e.g. retrospective DHF (available for audit, need not be renamed)
Practical implementation of device Design Controls (Continued)

- **Case Study**: PharmCo has been marketing a liquid oral drug kitted with a “Liquid Medication Dispenser” [Class I device; 880.6430; (oral syringe, dropper, cup, spoon)] exempt from Design Controls

- **Breakout discussions/ concerns**:
  - FDA is developing specific guidance to accompany final rule
  - Simple devices were discussed that had a range of non-obvious requirements e.g. measurement of high-density liquids
  - Device requirements for pediatric formulations are often developed late in the process since the dose range is not finalized
  - OTC drugs are not exempt from combination product requirements – see FDA OTC guidance (May 2011). Case study with OTC drug dose and syringe capacity mismatch.
  - What is being done for HFS for legacy products? FDA might accept commercial history if no change; note that device improvements are continually made
  - There are differences in FDA and industry expectations for product complaints and how to address them for different populations
Case Study: In an IND Type C meeting, PharmCo was asked by CDER to conduct formal Human Factors Studies (HFS) of a prefilled injector per FDA guidance and to study “patient handling” for usability in a clinical trial.

Breakout discussions/ concerns:
- Requests have been made from CDRH for HFS and from CDER for usability studies within clinical trials.
- This is a new field for many pharma companies therefore is very challenging.
- Device versions in summative HFS vs usability studies need to be clearly described including explanations for any changes made as device evolves in response to issues.
- Clear explanation required as to how the simulated HFS with experts mitigates risk such that separate usability studies in clinical trials might not always be necessary.
- Concerns expressed regarding conflicting information from HFS and clinical studies.
Design Validation: Human Factors Studies or Clinical Trials (Continued)

Case Study: In an IND Type C meeting, PharmCo was asked by CDER to conduct formal Human Factors Studies (HFS) of a prefilled injector per FDA guidance and to study “patient handling” for usability in a clinical trial.

Breakout discussions/ concerns:

- Concept of “least burdensome” for devices does not exist for drugs and therefore does not exist for combination products (unless CDRH is the lead center).
- FDA’s request for usability studies is not to assess success but to determine risks associated with task failures.
- CDER needs to assess actual conditions of use e.g. home setting.
  - However, both HFS and clinical trial studies might not represent real-world.
- Device explanations are critical e.g. use of videos.
- Complex environment exists for regulators working across centers.
- Timing constraints imposed by necessity of doing usability studies on final device in Phase 3 studies.
Developing and justifying delivery device specifications

Case Study: A delivery device “actuation button” force specification needs to be established among other technical specifications –some of which may be release specifications.

Breakout discussions/ concerns:

- Device performance attributes are typically set up during design controls (e.g. from HFS) vs drug specifications that are set based on batch analysis.
- The initial starting point is based on patient population, drug profile, potential risks, indication, prior knowledge. The specification could then change based on experience with the combination product.
- Product quality specifications can be set based on performance and consistency, rather than solely on batch data i.e. consider batch data as well as qualification limits (as is the trend for drugs)
  - Could have two types of specifications – one based on performance and one to control variability, e.g. PFS glide specification.
Case Study: A delivery device “actuation button” force specification needs to be established among other technical specifications –some of which may be release specifications.

Breakout discussions/ concerns:

- Consider the impact of the specification e.g. safety, efficacy. Attribute risk assessment should be performed – is it a CQA?
  - Consider practical significance vs statistical limits
- Application of QbD to combination products was discussed
  - Specifications are only part of the control strategy
  - Improvements in devices are made over time
  - Implications for post-approval changes in control strategy
Case Study: PharmCo has a joint venture with DeviceCo to develop an antimicrobial coating for DeviceCo’s implant. PharmCo needs to advise DeviceCo how to comply with the relevant Combo cGMPs in the implant’s development.

Breakout discussions/ concerns:

- DeviceCo will keep QSR as umbrella regulation, and implement 210/211 into their Quality system.
- This is a collaboration – teamwork is essential such that PharmCo supports the development at DeviceCo.
- Storage of reserve samples is required. Cost and space issues were discussed.
- Design of necessary stability studies and conditions is critical. Need to assess the relevance of stability-indicating tests
  - Is the solid form of the API different? What is done to the API e.g. terminal sterilization that will have an impact on the finished product? Are there compatibility issues?
  - Is a change in methods necessary? New CQAs?
Supporting device development with your drug product (Continued)

- **Case Study**: PharmCo has a joint venture with DeviceCo to develop an antimicrobial coating for DeviceCo’s implant. PharmCo needs to advise DeviceCo how to comply with the relevant Combo cGMPs in the implant’s development.

- **Breakout discussions/ concerns**:
  - For terminally sterilized combination products, one can release on the basis of negative biological indicator rather than routine release testing per lot.
    - Sterility needs to be evaluated on stability.
  - Analytical testing (release or stability) can potentially use a “representative” or surrogate device that is smaller (per consultation with FDA).
    - Stability testing can matrix multiple models/versions with appropriate justification.
  - Calculation of yield is typically done for consistency purposes and as part of the control strategy
    - There is not necessarily a regulatory expectation to maximize the yield.
  - Timing of process validation of combination products was discussed