Drug Product Quality Tips: Drug-Device Combination Products

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Day 2, April 13
Learning Objectives

• Define drug-led combination product
• Describe the framework for quality assessment
• Discuss product development studies to demonstrate suitability for use
• Discuss quality control and stability program
Combination Product

• A combination product is a product composed of 2 or more different types of medical products (i.e., drug, device, and biological product) per 21 CFR part 3.

• Subject to 21 CFR part 4 subpart A, Current Good Manufacturing Practice Requirements for Combination Products (2017) (out of scope)
  – Drug CGMPs: 21 CFR parts 210 and 211
  – Device Quality System regulation: 21 CFR part 820

• Generally, combination products include:
  – Single entity (e.g., drug in a prefilled syringe)
  – Co-packaged (e.g., drug vial packaged with a syringe)
  – Cross-labeled, i.e., packaged separately but labeled for use together
Current Premarketing Pathways

- **Device-Led Combination Products**
  - Premarket approval applications, De Novo Classification Requests, Premarket Notification (510k) submissions

- **Drug-Led Combination Products**
  - New Drug Application (NDA),
  - Abbreviated New Drug Application (ANDA)

- **Biologic-Led Combination Products**
  - BLAs under 351(a)
  - BLAs for Biosimilar and Interchangeable biological products under 351(k)

Reference: Principles of Premarket Pathways for Combination Products | FDA
Drug-Led Combination Product

• Assign based on which constituent part provides the primary mode of action (PMOA).

• PMOA is the single mode of action that provides the most important therapeutic action.

• For drug-Led combination product, PMOA is attributed to the drug.
  – CDER is the lead center that will have primary jurisdiction for its premarket review and regulation.
Drug-Led Combo Product Examples

- **Parenteral:** IV bag, prefilled syringe, injector (pen, jet, auto-injector, on body injector)
- **Oral:** oral administration devices (dropper/syringe/cup that measure dose)
- **Ophthalmic:** eye dropper
- **Nasal:** nasal spray
- **Inhalation:** metered dose inhaler, dry powder inhaler
- **Topical:** transdermal and topical delivery system, metered pump
- **Vaginal:** vaginal system (ring), vaginal applicator
DP Quality Framework – ICH Guidance

- **M4Q: The CTD — Quality (2001):** 3.2.P.2.4 reproducibility of the dose delivery from the device presented as part of the drug product (DP)

- **ICH Q1A(R2) Stability Testing:** 2.2.5 functionality tests (e.g., for a dose delivery system)

- **ICH Q6A Specifications:** 3.3.2.3 (j) Functionality testing of delivery systems: Parenteral formulations packaged in prefilled syringes, autoinjector cartridges, or the equivalent should have test procedures and acceptance criteria related to the functionality of the delivery system...

- **ICH Q8(R2) Pharmaceutical Development**

- **ICH Q9 Quality Risk Management**

- **ICH Q10 Pharmaceutical Quality System**

- **Draft ICH Q12: Implementation Considerations for FDA-Regulated Products (2021):** provide a framework to facilitate the management of post-approval CMC changes, including Appendix A for combination products with device constituent parts
DP Quality Framework – FDA Guidance

- Container Closure Systems for Packaging Human Drugs and Biologics, 1999
- Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation, 2002
- Glass Syringes for Delivering Drug and Biological Products: Technical Information to Supplement International Organization for Standardization (ISO) Standard 11040-4
- Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products, 2013
- Current Good Manufacturing Practice Requirements for Combination Products, 2017
- Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Products - Quality Considerations (Rev.1), 2018
- Transdermal and Topical Delivery Systems - Product Development and Quality Considerations (Draft), 2019

Note: EMA Guideline on the quality requirements for drug-device combinations (Draft), 2019
Quality Assessment process of ANDA

• OPQ assessment team
  – Assess drug substance/product, manufacturing (process and facility inspections), biopharmaceutics, and microbiology quality aspects of an ANDA application.

• OGD assessment team
  – Bioequivalence
  – Comparative threshold analyses studies (impact of device differences on user interface)*
  – Labeling (except description and how supplied/storage conditions)

*Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA: Draft Guidance for Industry | FDA
CDRH consults

• May be requested based on **combination product risk profile**
  – e.g., emergency-use product, technologically complex device constituent parts, like auto-injector

• Request via ICCR (intercenter consult request) process

• 1) Device Engineering/Performance
  – Design control including essential performance requirements (EPRs)/drug delivery functions; design verification & validation; performance data, etc.

• 2) Device Quality System regulation/Facilities Assessment (21 CFR part 820)
DP Development (P2) - QTPP

- Establish QTPP to ensure the desired quality, taking into account safety and efficacy of the product.

- Provide rationale for the selection or design of the proposed container closure system (CCS), including the device constituent part.

QTPP elements can include device specific aspects, functional property requirements* of device constituent part.

<table>
<thead>
<tr>
<th>QTPP Elements of Autoinjector ANDA</th>
<th>Target</th>
<th>Justification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage Form</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Route of administration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strength</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DP quality attributes (e.g., purity, sterility)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stability</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCS, including the device constituent part</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Device functional property requirements</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Transdermal and Topical Delivery Systems - Product Development and Quality Considerations | FDA
DP Development (P2) - CQA

• Identify critical quality attributes (CQAs) that are physical, chemical, biological, or microbiological properties that should be within appropriate limits with justifications.

• Use prior knowledge and risk assessment to identify critical material attributes (CMA) and critical process parameters (CPP) that have potential impacts on CQAs

• Modify CQAs as new knowledge is gained.

• Include more product specific aspects (e.g., sterility for a parenteral product).
DP Development – CCS Suitability (P2)

• To qualify your proposed CCS, demonstrate suitability for its intended use:
  – Adequately protect the dosage form, such as oxygen, loss of solvent, microbial contamination, light (ICH Q1B)
  – Compatible with the dosage form
  – Composed of materials that are considered safe for use with the dosage form and the route of administration
  – Function properly for a performance feature
Compatibility Study

• A dosage form should not interact with the packaging components to cause unacceptable changes in quality
  – e.g., glass delamination study (USP <1660>); in-use stability/compatibility study (in-use duration and temperature per labeling).

• Consider all materials that are/may be in contact with the drug product.

• Potential Physical and Chemical Compatibility:
  – Loss of potency due to absorption/adsorption of API
  – Degradation of the API (e.g., a compound from the adhesive used to fix the needle in staked-in needle prefilled syringe)
  – Changes in drug product pH
  – Discoloration
  – Precipitation
Extractables and Leachables

• Packaging components should not leach harmful or undesirable amounts of substances.
  – Any packaging components which may be in direct contact with the dosage form
  – Any components from which substances may migrate into the DP (e.g., ink, glue).

• Conduct per USP <1663> and <1664>

• Assess based on Analytical Evaluation Threshold (AET) calculated from max. daily dose and Safety Concern Threshold (SCT) or Qualification Threshold (QT)

• Identify and provide toxicological assessment for any leachables above the AET

• Current FDA Thinking for all routes (excluding orally inhaled, nasal (SCT = 1.5 µg/day); epidural or intrathecal; and topical ophthalmic):
  – Chronic Duration of Use: SCT = 1.5 µg/day
  – Less than Chronic Duration of Use: QT = 5 µg/day
Performance/Functionality

• Performance of the CCS refers to its ability to function in the manner for which it was designed.

• Demonstrate the ability of the device to deliver the product in an accurate and reproducible way (e.g., dose) [Q8(R2)].

• Simulate the use of the DP closely for test condition [Q8(R2)] (per labeling).
Performance/Functional Test Examples

- Prefilled Syringe
  - Delivered volume accuracy
  - Breakloose force
  - Glide force

- Auto-injector
  - Dose accuracy
  - Cap removal force
  - Activation force
  - Extended needle length
  - Injection time

Ref: Figures above are from the package insert (Drugs@FDA: FDA-Approved Drugs) and for illustration purposes only.
Case Study: Dose Accuracy Study

<table>
<thead>
<tr>
<th>Drug Product and Device Constitute Part</th>
<th>A 2.8 mL fill multiple dose vial is co-packaged with 14 disposable syringes and needles as 14-Day Patient Administration Kit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Label Directions</td>
<td>Inject each daily dose of 0.2 mL per day (for 14 days)</td>
</tr>
</tbody>
</table>
| Study Design                          | To stimulate the use of the DP per labeling,  
• Evaluate for accuracy of each dose from each of the 14 syringes provided in the kit.  
• Evaluate if a total of 14 doses can be withdrawn from one vial. |
Control of Combo Drug Product (P5)

- Design a control strategy to ensure that a product of required quality will be produced consistently.
- Develop based on product risk profile (e.g., complexity of design and manufacturing)*.
- Tests and acceptance criteria should be appropriate to the particular dosage form, route of administration, and design features.
- The performance test methods should follow the compendial USP (e.g., USP <697) and recognized ISO testing standards, as applicable
  - e.g., 11608-1 to 6: Needle-based injection systems for medical use - Requirements and test methods (CDRH recognized standards)
  - FDA database: Recognized Consensus Standards (fda.gov)

*Reference: Transdermal and Topical Delivery Systems - Product Development and Quality Considerations | FDA
# Drug Formulation Specs (P5)

<table>
<thead>
<tr>
<th>Attributes for DP Solution in Autoinjector</th>
<th>USP Chapter</th>
<th>Release</th>
<th>Stability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description (Color, Clarity)</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Identification</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Assay, Impurities</td>
<td>&lt;621&gt;</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>pH</td>
<td>&lt;791&gt;</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Particulate Matter</td>
<td>&lt;788&gt;</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Visible Particulates</td>
<td>&lt;790&gt;</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Sterility</td>
<td>&lt;71&gt;</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Bacterial Endotoxins</td>
<td>&lt;85&gt;</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Container Content</td>
<td>&lt;697&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meet general chapter requirements</td>
<td>&lt;1&gt;, &lt;467&gt; (option 1 or 2)</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

Others: osmolality, viscosity, preservative, critical excipients (e.g., antioxidant), as applicable
# Device Performance Specs (P5)

<table>
<thead>
<tr>
<th>Attributes for Device Constitute Part of Autoinjector</th>
<th>Release</th>
<th>Stability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description of Device Constitute Part</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>- Freedom from defects (e.g., displaced parts, cracking, leaking)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose accuracy</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>cap removal force</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Activation force</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Extended needle length</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Injection time</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

- Acceptance criteria along with justifications should be provided.
- Report the value only may not be acceptable for QC control.
Container Closure System (P7)

- Description of primary and secondary packaging components and device constituent part: materials of construction, manufacturers, DMF # (LOA), coating, lubricant, etc.

- Suitable QC specifications and test procedures, including description, I.D., critical dimensions, and functional tests, as relevant.

- Technical drawings, high resolution photographs, schematic diagrams (before & after use) of all packaging components.

- Certificates of Analysis (COA) from both supplier and drug product manufacturer

- Compliance with relevant USP chapters:
  - USP <87>/<88>, <381>, <660>, <661> or <661.1/661.2>, <671>

- Indirect food additive regulations (21 CFR 174-186)
Stability (P8)

- To support expiry, package as intended for marketing, store, and test per ICH Q1A(R2) & Q1E, including the device constituent part and the primary and secondary packaging component.
  - One full primary batch fully assembled and packaged (e.g., one primary batch is completely filled into cartridges, entirely assembled into pen-injectors, and placed in cartons)
  - The other two batches with sufficient fully assembled and packaged products for DP quality and performance stability testing
- Store in an inverted (or horizontal) & upright (or vertical) position to define the worst case position.
  - Can use one position for post approval stability testing if no differences are observed.

Ref: ANDAs: Stability Testing of Drug Substances and Products, Questions and Answers | FDA
Figure is from the package insert (Drugs@FDA: FDA-Approved Drugs) and for illustration purposes only.
Challenge Question #1

Which of the following products is NOT a drug-led combination product?

A. Drug in IV plastic containers
B. Drug in bottles with child-resistant closures
C. Drug in glass vials with empty syringes
D. Drug in aluminum tubes with vaginal applicators
Challenge Question #2

Which of the following statements is **NOT** true?

A. Auto-injector must comply with Current Good Manufacturing Practice Requirements for Combination Products.

B. CDRH assesses aging/stability data and specification for Essential Performance Requirement (EPR) of auto-injector.

C. Threshold of Toxicological Concern (TTC) of 120 μg per day can be used to calculate AET for assessing extractables and leachables of auto-injector due to treatment duration of < 1 month.

D. Stability data should demonstrate that the performance (specification) of auto-injector is maintained during shelf-life.
Summary

• Discussed DP quality considerations for generic combination products in terms of suitability for use.
• Discussed control of DP and stability requirements.
• With increasing in complexity and innovation of combination products to advance patient care, more guidance will be developed to address a regulatory submission.
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Questions?

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