Drug Product Quality Tips: Drug-Device Combination Products

SBIA 2023: Celebrating 10 Years of the FDA Generic Drugs Forum (GDF) 2023

Day 2, April 13

Kai Kwok, Ph.D.

Senior Pharmaceutical Quality Assessor

Division of Liquid-Based Drug Products, Office of Lifecycle Drug Products/Office of Pharmaceutical Quality

CDER | U.S. FDA

Celebrating 10 Years of the GDF – April 12-13, 2023

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)

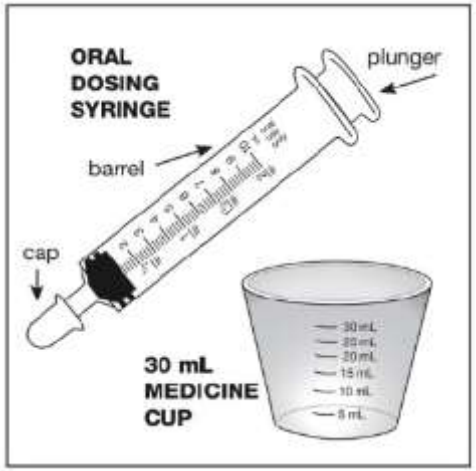
Reference: Principles of Premarket Pathways for Combination Products | FDA

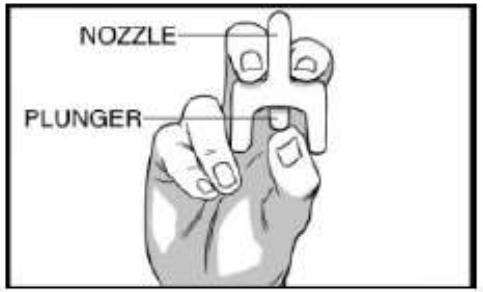
Drug-Led Combination Product

- 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.

QTPP Elements of Autoinjector ANDA	Target	Justification
Dosage Form		
Route of administration		
Strength		
DP quality attributes (e.g., purity, sterility)		
Stability		
CCS, including the device constituent part		
Device functional property requirements		

*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**

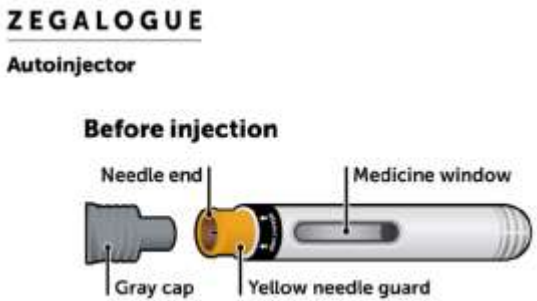
Performance/Functionality

- 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

Drug Product and Device Constitute Part	A 2.8 mL fill multiple dose vial is co-packaged with 14 disposable syringes and needles as 14-Day Patient Administration Kit
Label Directions	Inject each daily dose of 0.2 mL per day (for 14 days)
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)

Attributes for DP Solution in Autoinjector	USP Chapter	Release	Stability
Description (Color, Clarity)		X	X
Identification		X	
Assay, Impurities	<621>	X	X
pH	<791>	X	X
Particulate Matter	<788>	X	X
Visible Particulates	<790>	X	X
Sterility	<71>	X	X
Bacterial Endotoxins	<85>	X	X
Container Content	<697>	X	
Meet general chapter requirements	<1>, <467> (option 1 or 2)	X	
Others: osmolality, viscosity, preservative, critical excipients (e.g., antioxidant), as applicable			

Device Performance Specs (P5)

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

- 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.

Acknowledgement

- Office of Lifecycle Drug Products
- Hailing Zhang
- Pahala Simamora
- Andre Raw
- Geoffrey Wu

U.S. FOOD & DRUG ADMINISTRATION

Questions?

Kai Kwok
Senior Pharmaceutical Quality Assessor
Division of Liquid-Based Drug Products,
Office of Lifecycle Drug Products/Office of Pharmaceutical Quality
CDER | U.S. FDA