Regulator’s Perspective on Combination Products

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What is a Combination Product?

- Defined in 21 CFR 3.2(e)
  - Physically or chemically combined (prefilled syringes)
  - Co-packaged in a kit
  - Separate, mutually consentingly cross-labeled products

- Combinations of different types of products (involve different CENTERS at the FDA):
  - Drug-device
  - Device-biologic
  - Drug-biologic
  - Drug-device-biologic
  - Not drug-drug, device-device or biologic-biologic combinations
  - Not a food or cosmetic
Primary Mode of Action (PMOA) Defines the Lead Center for the Combination Product Determination Made by Office Of Combination Products (OCP) via RFD Process (Request for Determination)

Primary mode of action is the single mode of action of a combination product that provides the most important therapeutic action of the combination product. The most important therapeutic action is the mode of action expected to make the greatest contribution to the overall intended therapeutic effects of the combination product. 21 CFR 3.2(m)

Contact OCP: Combination@fda.gov or call 301-796-8939
PMOA -- CDER or CDRH?

**Drug Eluting Stent**

- **Primary Mode of Action:** Stent opens artery
- **Secondary Action:** Drug prevents inflammation and restenosis of artery
- Regulated by CDRH under device provisions

**Drug Eluting Disk**

- **Primary Mode of Action:** Cancer chemotherapy for brain tumor
- **Secondary Actions:** Local drug delivery of drug by device
- Regulated by CDER under drug provision
Where Are Prefilled Devices Regulated?

• Typically, prefilled glass syringes or injectors (device) deliver drug or biologic products
• By regulation (21CFR3.2(e)(1)), the drug/biologic prefilled in devices are considered combination products
• Assigned to CDER or CBER as the lead center due to PMOA (therapeutic effect on the body)
• Marketed under one application (NDA, BLA, or as a generic equivalent)
OCP

CDRH

CDER

CBER
General Hospital Devices Branch
Approx. 500 consults for CDER/CBER in 2014
ODE/GHDB Staff and Expertise
Branch Demographics

- Nurse Consultants: 23% (4)
- Bio/Mechanical Engineers: 29% (5)
- Software Engineers: 24% (4)
- Medical Officers: 18% (3)
- PharmD: 6% (1)
GHDB - Device Product Areas

GHDB

Medication
Adherence/Reminder

RX
Why are prefilled syringes heavily reviewed by CDRH now? History is important.


- **Nov 2010, May 2011, Sept 2013** FDA Issued Public Health Advisories
- **AUDIENCE**: Critical Care Medicine, Emergency Medicine, Cardiology, Risk Manager
- **ISSUE**: FDA is notifying healthcare professionals, especially those working in emergency and critical care settings, of reports of compatibility problems when certain needleless pre-filled glass syringes are used with some needleless intravenous (IV) access systems. These syringes may malfunction, break, or become clogged during the process of attempting to connect to needleless IV access systems.
Prefilled Glass Syringe Common Issue

- Several of the prefilled glass syringes utilized the same or similar types of glass syringe.
- Post-market safety reports were received related to failure to deliver the drug, breakage of the syringe tip, breakage of needleless connector, failure to securely lock to a needle.
- Evaluation of these events indicated that a large number of products may have similar defects.
Adenosine Prefilled Syringes

- Adenocard is the originator Reference Listed Drug
- Adenocard RLD was first approved as a prefilled glass syringe and later changed to a plastic syringe design due to a safety reason.
- One of the firm’s reasons for the change is "[t]he use of plastic syringes avoids potential breakage, especially in emergency situations". (9-21-01)
Possible Root Causes

• Some glass syringes were designed for injection, not for connection to IV lines to achieve IV push. Syringe Tip Inner Diameter is Too Small and May Break with Pin Piercing LAV (Luer Activated Valves) as depicted in the diagrams below.

• Outer diameter of the glass syringe nozzle may be slightly too large or do not conform to ISO 594 specifications and may lead to glass breakage when screwed into the needleless connectors.

• Glass syringe nozzle length that is too long can lead to glass breaking in the IV connector when clinician trying to tighten the connection in order to push the medication. Or the nozzle length is too short so it cannot activate the spring to open the valve to push the medication through which prompts the nurse/doctor to further tighten the syringe screw into the connector and results in glass breaking thus downing the IV line.
Syringe Tip Inner Diameter is Too Small and May Break with Pin Piercing LAV (Luer Activated Valves)
The Syringe Dimension Incompatibility with Pin-Activated Luer Connectors Can Cause the Pin Tip to Break and Clog the Syringe Outflow

http://www.fda.gov/Drugs/DrugSafety/ucm254215.htm

Figure 1.

the pin from the access system became clogged
Incompatibility between the Glass Syringe and the Pin-Activated IV Luer Connectors are not Detected until the Syringe is Actually Inserted into the Luer Connectors.

http://www.fda.gov/Drugs/DrugSafety/ucm254215.htm
Note: Glass Syringe Standard ISO 11040-4 Allows Deviation from the Luer Standard ISO 594

Annex A
(informative)

Head designs

Dimensions in millimetres

\[ \phi_{d_6}^{a} \]

\[ \phi_{4.4 \pm 0.07}^{b} \]

\[ \pm 0.01 \]

\[ \pm 1.5 \]

\[ 7.5 \]

\[ a \times \]

Agreed between customer and manufacturer.

\[ b \]

Tolerance deviating from ISO 594-1.
Prefilled Glass Syringe

• Prefilled syringes are combination products and thus the testing should be performed on the final-finished assembled product filled with the drug/biologic.
• Performance testing should take into consideration the viscosity of the drug, resistance created by the fluid contact path, and the back pressure/shear force generated during the injection as to whether it could alter the characteristic, functionality, safety and effectiveness of the drug/biologic.
• Drug/biologic compatibility/reactivity with the lubricant used in the syringe barrel.
• In addition, evaluate whether the back pressure generated could detach the needle from the syringe during the injection.
These data should include, but are not limited to, the following:

- Leak Testing – liquid leakage, air ingress, dye ingress
- Glide Force
- Break Force
- Separation Force
- Unscrewing torque
- Ease of Assembly
- Resistance to Overriding
- Stress Cracking
- Validation of Graduation Markings
- Dead Space
- Coring Needle Test
- Performance of anti needle stick mechanism per CDRH guidance on Needle Stick Prevention Mechanisms (i.e., 500 devices tested with numerous activations, zero failures to establish 99% confidence interval of the device's safety / effectiveness).
- Connectivity to other devices necessary for use (e.g., needles, adapters, transfer systems, extension tubing, luer connectors)
- Appropriate ISO standards (11040-4, 594-1, 594-2, 7864 and etc.)
Drug or Biologic using Injectors/Prefilled Syringes Assembled into Injectors

Guidance Document (finalized 2013):
Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products

  
  – Covers a continuum of pen, jet, and related injectors
  – General use, common device platform, and combination products;
  – Considerations for injectors provided in NDA, BLA, PMA, or 510(k)
  – Addresses scientific and technical issues
  – Roadmap for injector submissions
Product Development Considerations

- Are the constituent parts already approved for an indication?
- Is the indication for a given constituent part similar to that proposed for the combination product?
- Does the combination product broaden the indication or intended target population beyond that of the approved constituent part?
- Does the combination product expose the patient to a new route of administration (such as jet injection as the route of delivery) or a new local or systemic exposure profile for an existing indication?
- Is the drug formulation different than that used in the already approved drug?
- Does the device design need to be modified for the new use?
- Is the device constituent used in an area of the body that is different than its existing approval?
Product Development Considerations

• Is there any other change in design or formulation that may affect the safety/effectiveness of any existing constituent part or the combination product as a whole?
• Is a marketed device being proposed for use with a drug constituent that is a new molecular entity?
• Is a marketed drug being proposed for use with a complex new device?
Common Device Considerations

It may be appropriate to conduct studies to evaluate the potential for the following:

- Leachables/extractables of the device materials into the drug/biologic substance or final combination product;
- Drug constituent when delivered by the device or when used as a coating on the device and could that interaction impact on the device performance;
- Drug adhesion/absorption to the device materials that could change the delivered dose;
- Presence of inactive breakdown products or manufacturing residues from device manufacture that may affect safety, or device actions that could change the drug performance characteristics at the time of use; or
- Changes in the stability or activity of a drug constituent when used together with an energy emitting device.
Common Device Consideration
Human Factors

• Intended user population (arthritic or blind)
• Environment of use (lay people at home)

For example, a product started as a prefilled syringe used by healthcare professionals that later morphed into prefilled autoinjectors used by adult lay users at home (which would definitely trigger a need for HF study) and then the drug is seeking a pediatric indication still using the same autoinjector (also definitely need HF).
Green Injector to Deliver Both Short and Long-acting Insulin---Human Factors???
Consistent Device Information Layout to Facilitate Review

- **Device description** (list all materials of construction including adhesives, color additives, cross-linkers and etc.)
- **Pictures/engineering drawings** of assembly and subassembly
- **List all standards** your device conforms to
- **Principle of Operation** of the Combination Product
- **Biocompatibility** (consider material-mediated sensitivity leading to pyrogenicity)
- **Sterilization method and validation method** as well as packaging
- **Shelf Life** and associated testing
- **Testing protocols and data**
  - bench,
  - animal,
  - clinical,
  - human factors,
  - software (see next slide for specific information format),
  - electrical/electromagnetic
- **Risk analysis and mitigation**
If Your Device Constituent has Incorporated Software

- Thoroughly Understand FDA Software Validation and Verification Guidance: http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm085281.htm
- State the software’s level of concern (minor, moderate, major)
- **Provide a complete description of your software, its functions and features. Include all warning/error messages**
- **Make sure that you have identified all hazards associated with the device.**
- Provide System Requirements Specification, Architecture Design, and System Design Specification. Be sure to provide detailed definition of all data fields used in your software, including definitions such as data type and ranges. Provide algorithms for all calculated fields.
- Describe your Software Development Environment. Including configuration and maintenance strategies. For example, provide life-cycle development methodology, how to handle change request, improvement, etc.
- **Provide your Validation and Verification Document. These documents should include your unit and system/integration testing. Your test cases should include description, steps, acceptance criteria, and test results.**
- Provide a list of any unresolved anomalies (bugs) remain in your system. This list should also contain information such as detailed description of the symptom, cause, impact on safety and effectiveness, work around, estimated resolution date, etc.
- Also provide your revision history so we will be able to clearly understand the changes/new features you are making to the software.
- **Traceability Analysis provide clear and concise links amongst identified hazards, product design requirements, testing and test results to demonstrate that all identified hazards are properly mitigated.**

One example of such information can be provided in the following table.

<table>
<thead>
<tr>
<th>Haz ID</th>
<th>Cause(s)</th>
<th>Risk level before mitigation</th>
<th>Risk level after mitigation</th>
<th>Requirement and/or mitigation desc/ID</th>
<th>Design desc/ID</th>
<th>Test Desc /ID.</th>
<th>Test Result (P/F)</th>
</tr>
</thead>
</table>
Where to Put the Device Information in the Electronic Submission to CDER/CBER

eCTD options for including device information

- Provide a Table of Content with device subsection(s); reviewer roadmap; summary of CP as a whole, constituent parts; focus areas (e.g., human factors, manufacturing)
- Providing a "Information to Reviewers" or “Reviewers Guide” document in Module 1.2 Cover letters can be helpful
- Device-drug quality summary; module 2.3
- Device details: quality module 3 (usually under 3.2.P.7)

When including and referencing device information:

- You may reference files under 3.2.P.7 which are not currently listed as numerical items in ICH and FDA specifications and guidance.
- In 3.2.P.7 you could include a leaf titled something similar to the following, “Table of Contents for Drug-Device Autoinjector. This leaf/document, could provide reference links to the other files in module 3.2.P.7. Obtaining concurrence from the Review Division on the proposed outline is recommended.
- The leaf titles should be clear, concise and indicative of the document's content.
Application Submission to FDA

- Generally only one application to the lead center which should include all information for all constituent parts
  - DMF or cross reference to existing application for proprietary data that cannot be included in IND/IDE (need a Letter of Authorization)
  - Request milestone meetings to include all relevant centers, all key manufacturers, OCP as appropriate
  - FDA only needs one marketing submission for most combination products (submissions to different Centers have lead to delay)
  - FDA can require two submissions; 21 CFR 3.4(c)
  - Some firms may request two when one is sufficient. FDA will decide on a case-by-case basis
Key Steps to Successful Application

- Determine classification and lead center (start the discussion with FDA via a pre-submission)
- Early Pre-IND/IDE meeting with all involved centers, OCP, and industry development partners
- Identify any product changes you anticipate; steps to document changes, and effect on safety or effectiveness
- Discuss number of marketing applications that may be appropriate and what data should be in which
- Discuss any proprietary data issues (master file)
- Labeling and human factors study (studies to see if user can comprehend and follow the IFU)
- Post-approval changes anticipated
Lessons Learned

• 510K cleared device does not mean CDRH will not review the device constituent at the time of NDA/BLA review.
• Consider using plastic syringe vs. glass syringe to avoid the known clinical pitfalls.
• Consider using a Master File for the device information review because it is not restrained by the MDUFMA clock as in the case of 510K submission.
• 510K cleared device may still need an inspection before NDA/BLA approval.
• Platform device that is used again and again should have testing for the modifications made to suit the different drug/biologic (consider the dosing, viscosity of the drug/biologic, the population of use and environment of use).
• Platform devices used for same patient population should have distinguishing features for easy differentiation.
• If the device is in cold storage every day and expected to be used for 2 years then provide testing on the bench and tracking during clinical trial to demonstrate that prolonged cold exposure does not degrade the combination product’s performance.
• Test the FINAL-FINISHED combination product as a whole! For example, changing to a thinner needle to decrease pain will result in increased back pressure. Will that cause needle detachment or shear the biologic on exit?
• Track the device failures/malfunctions during the clinical trials.
• Do not submit a device application for a general use indication if there isn’t a drug/biologic already approved/labeled for the device or that route of administration.