Quality Considerations for Injectable Drug-Device Combination Products in Abbreviated New Drug Applications (ANDAs)

AAM 2020: GRx+Biosims Complex Workshop

Session 4: Device Considerations for Complex Drug-Device Combination Products

Richard Chang, PhD

Division of Liquid-Based Products, Office of Lifecycle Drug Products
Office of Pharmaceutical Quality | CDER | U.S. FDA

November 10, 2020

Injectable Drug-Device Combination Products

- Injectable combination products can be in various package/co-package designs.
- It can be co-packaged with the drug constituent part (e.g., Octreotide vial co-packaged with vial adapter, needle, and prefilled diluent syringe for acromegaly and diarrhea) or it can be distributed separately but labeled for use together.
- Devices can be pre-filled with the drug constituent part:
  - pre-filled syringe (PFS), e.g., Copaxone PFS (Glatiramer acetate for multiple sclerosis), Rosinox-40 PFS (Enoxaparin sodium for anticoagulation), Roshep-10 PFS (Heparin sodium for anticoagulation)
  - pen injector (using cartridge system for multiple doses with manual mode injection and replaceable needle component), e.g., Forteo pen injector (Teriparatide for osteoporosis), insulin pen injector (insulin for diabetes)
  - auto injector (using spring loaded injector with automatic mode and shielded needle tip as passive safety mechanism), e.g., EpiPen (Epinephrine for anaphylaxis, prefilled, single emergency use)
- These drug-device combinations may be designed as single use, disposable, reusable, single dose, multiple dose or adjustable dose.

Delineating Review Responsibility for Drug-Device Combination Products

- Based on primary mode of action (PMOA, i.e., the most important therapeutic action), Center for Drug Evaluation and Research (CDER) will be the lead center for the drug-device combination products with drug as PMOA; Center of Biologics Evaluation and Research (CBER) will be the lead center for biologics-device combination product; and Center for Device and Radiological Health (CDRH) will be the lead center for device with drug/biologics.
- Assessment of the user interface will be assigned to OGD Division of Clinical Review.
- Through inter-center consult request (ICCR), CDRH will be responsible for engineering device design evaluation. If necessary, CDRH is also responsible for facilities/manufacturing assessment through ICCR.
- CDRH will cover device performance and reliability analysis, device performance on stability, essential performance requirements (EPRs), control strategy, quality system assessment,[1] and biocompatibility of patient contacting components or materials that are not drug contacting (conformance to ISO 10993 with a combination of physicochemical, analytical and biological testing as appropriate).

1. ISO 11608-4 specifies requirements and test methods for electronic and electromechanical pen injector; ISO 11608-5 specifies requirements and test methods for automated injection systems, such as auto-injector.

   Note: All the tests should either meet the acceptance criteria or declare conformance to ISO regulations for all relevant test parameters.

Quality Considerations for Drug Constituent Parts

- USP <1> Injections and implanted drug products-product quality tests: identification, assay, impurities, foreign and particulate matter (USP <788> and visible particulate (USP <790>), Sterility (USP <71>, bacterial endotoxins (USP <85> or USP <151>), container content for injection (USP <697>), container integrity, and uniformity of dosage units (USP <905>).
- Drug constituent parts can vary significantly from solution, suspension, emulsion, lyophilized cake, to powder fill. Other product quality attributes should be monitored, e.g. globule size for emulsion, particle size distribution and dissolution test for suspension, and water content and reconstitution time for lyophilized cake or powder fill. pH, osmolality, viscosity, specific gravity, preservative content and anti-oxidant assay also should be considered to be included in drug product specification, if appropriate.
- Other than these drug product tests, packaging system needs to meet the following testing requirements to maintain the drug product's identity, strength, quality, purity and stability:

Elastomeric closures for injections (USP <381>), container-glass (USP <660>, plastic packaging systems and plastic materials of construction (USP <661), Containers-performance testing (USP <671>, extractable/leachable (USP <1663> and <1664>), and biological reactivity tests, in vitro (USP <87>)/biological reactivity tests, in vivo (USP <88>)

- Drug/Device compatibility including pre-filled cartridges and staked in needles
- Container-closure integrity test to ensure no contamination or loss of contents (USP <1207>)
- Residual solvents test (USP <467>) and elemental impurities (USP <232/233>) are required as well to meet the regulatory requirement.

Quality Considerations for Drug Constituent Parts

- **For stability orientation requirements**, generic companies should follow Guidance for Industry ANDA submission and stability testing to have stability data for both worse-case scenario (inverted or horizontal position) and non-worse-case situation (upright or vertical position) to avoid refuse-to-receive.[1,2] The applicant may propose different orientation setting for the stability testing from the guidance. However, it is recommended to obtain concurrence from the appropriate regulatory authority via controlled correspondence.
- **For number of API lots requirements**, a minimum of two lots of API should be used to prepare three primary batches of drug product. Note that mixture of two API lots to manufacture three drug product batches is not acceptable.[1]
- **For lots of packaging materials to support ANDA submission**, it is not necessary to use different lots of packaging material, except in cases where the packaging material could affect drug product quality and performance.[1]
- **For packaging of primary batches for ANDA submission**, it is recommended to have one primary batch using full manufacturing assembly run to fulfill drug product stability and device performance stability studies. The other two batches may be partial manufacturing assembly runs that produce sufficient final finished products to fulfill drug product stability and device performance stability studies, depending on manufacturing process and control strategy used.[3]

1. Guidance for Industry ANDAs: Stability Testing of Drug Substances and Products-Questions and Answers (May 2014)
2. Guidance for Industry ANDA submissions-Refuse-to-receive Standards (December 2016)
3. Guidance for Industry ANDAs: Stability Testing of Drug Substances and Products (June 2013)

Functionality Performance Test for Device Constituent Part (prefilled syringe)*

- Dose accuracy: e.g. 2.0 mL ± 0.1 mL
- Glide force: e.g. NMT 5 N, force to maintain plunger movement after break loose force
- Break loose force: e.g. NMT 15 N, force required to break static friction of plunger
- Leak testing: liquid leakage, air ingress, dye ingress
- Separation force: ISO 80369-7, Luer remains attached to the fitting when a maximum axial load is applied
- Unscrewing torque: ISO 594, Luer remains attached under a specific unscrewing torque
- Ease of assembly: ISO 594, assembly with minimum axial force and toque
- Resistance to overriding: ISO 594, the threads cannot be overridden by a specific screwing torque
- Stress cracking: ISO 594, Stress cracks occur at the center of the syringe barrel, which is a critical integrity issue.
- Validation of graduation markings: test requirement for markings on a syringe barrel or within a dispensing system (e.g. pen injector)
- Dead space: the space between the needle and the plunger
- Coring needle test: ISO 7864-Needle point magnification to verify no coring needle
- Connectivity to other devices necessary for use (e.g. needles, adapters, transfer systems, extension tubing, luer connector): ISO 594
- Tip cap removal force: ISO 1104-41 and e.g. LT 20 N
- Piston seal blowback (ability of syringe with tip cap to hold a certain pressure on the piston)
- Injection force necessary to depress the plunger and eject the drug content: ISO 11040-5: Plunger stoppers for injectables, e.g. LT 2.5 N
- Performance of anti-needle stick mechanism: per CDRH guidance on needle stick prevention mechanism

*Guidance for industry and FDA staff, Glass Syringes for Delivering Drug and Biological Products: Technical Information to Supplement International Organization for Standardization (ISO) Standard 1104-4

Functionality Testing and Essential Performance Requirements for Device Constituent Part (pen injector and auto injector)

Functionality Testing: Dose accuracy, flow rate, injection time, reliability of the mechanism to deliver the drug product, depth of injection, safety features, verification for absence of leakage, verification of no-coring needle, needle dwell time, chemical resistance, and structural testing at extreme pressure and temperature conditions.[1]

Mechanical specification assessment: force required for assembly, force required to actuate the injector, force required to defeat the needle shield or other safety mechanism, load testing on individual components, needle bond strength, needle penetration force, and needle deflection angle that causes injector failure.[1]

Essential Performance Requirements (as an example for auto-injector, ISO 11608-5**)**

- Delivered dose accuracy using the final combination to demonstrate the volume/weight of drug product expelled through the injector remains the same as the set dose.
- Force required for actuate the injector, i.e., activation force.
- Injection time, i.e. time required to deliver the drug product to the body.
- Extended needle length and depth of injection test results demonstrating reliable and reproducible depth of delivery using human, porcine or cadaver model.
- Cap removal force (emergency use) and visual/audible feedback (if in the device design).

1. Guidance for Industry and FDA Staff: Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drug and Biological Products (June 2013)
2. Note: All the tests should either meet the acceptance criteria or declare conformance to ISO regulations for all relevant test parameters.


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