Injectable Product Considerations from a Quality Perspective

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Pharmaceutical Quality

A quality product of any kind consistently meets the expectations of the user.




Drugs are no different.


FDA
Patients expect safe and effective medicine with every dose they take.

Pharmaceutical quality is

assuring *every* dose is safe and effective, free of contamination and defects.


It is what gives patients confidence in their *next* dose of medicine.

Objectives

- Discuss critical attributes of *Injectable Combination Products*
  - Functionality attributes
  - Quality attributes
- Provide points-to-consider for frequently asked questions

Why Injectors?

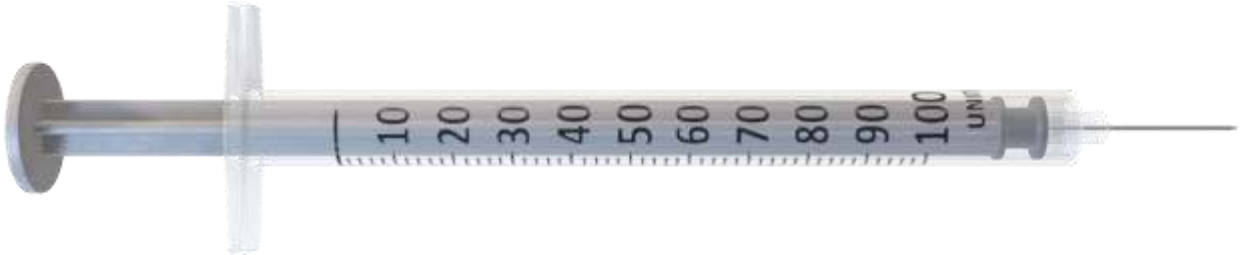
Usage Groups

- Wide range of drugs products (general injectors)
- Certain class/family of drugs products
- Specific drug product
  - Combination products under 21 CFR 3.2(e)

Injectable Combination Products

- Co-packaged with the drug product
- Separately distributed but labeled for use together
- Pre-filled with the drug product 
  - Pen injector, Auto-injector

Pre-filled Injectors



Single-use

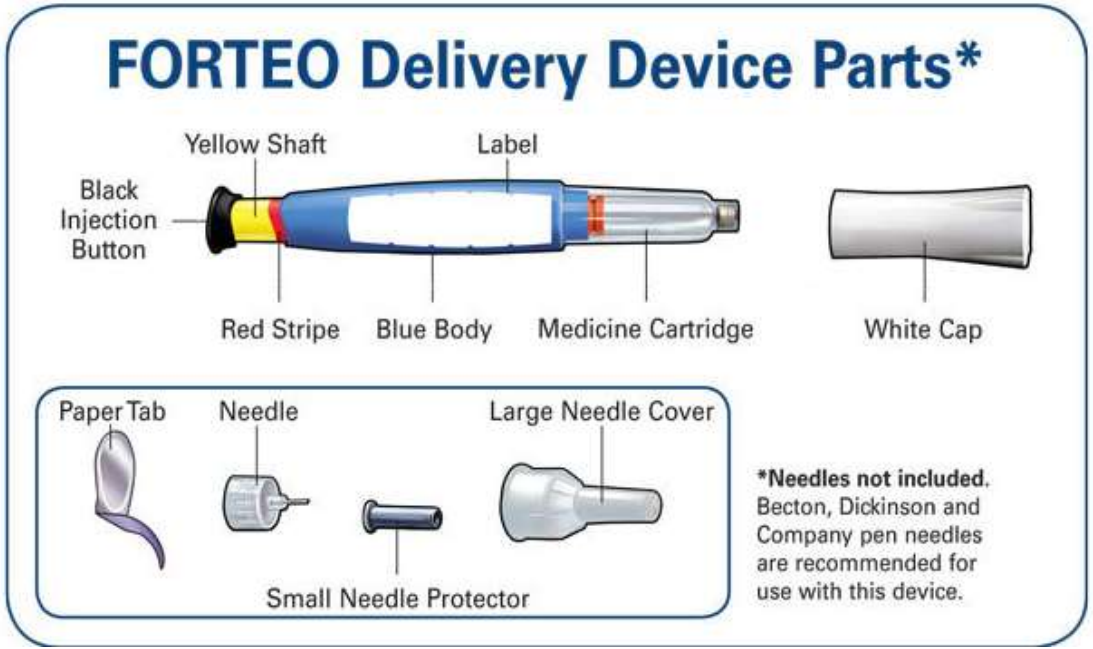
Disposable

Reusable

Single dose

Multiple dose

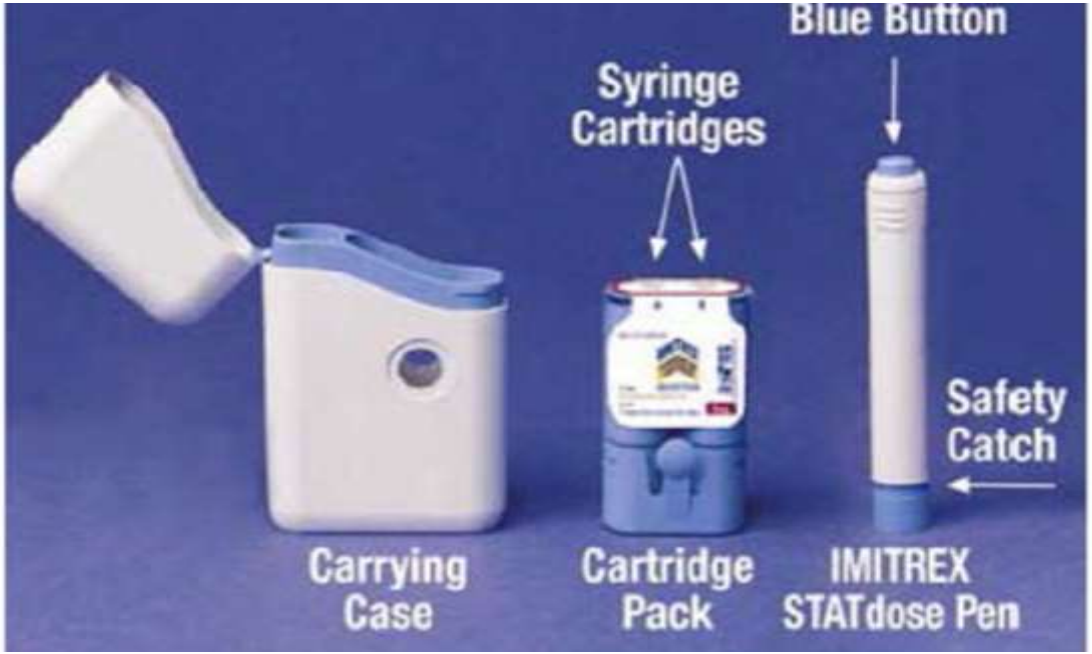
Adjustable dose



Pen Injector

Pre-filled, Multi dose, Disposable

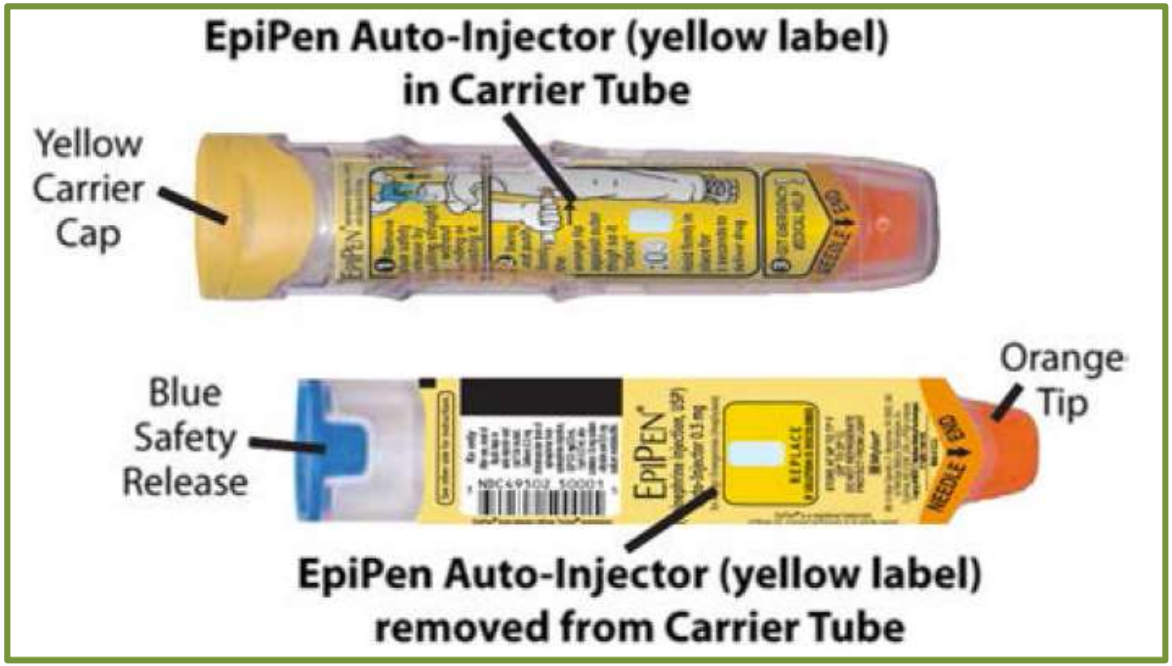
Source: http://uspl.lilly.com/forteo/forteo.html#mg



Pen Injector

Empty Pen, Reusable, Single-dose cartridges

Source: Drugs@FDA



Auto-injector

Pre-filled, Single-use, Emergency use

Source: Drugs@FDA

Prefilled Injectors

- **Pen injector**
  - Cartridge system
  - Multiple doses
  - Manual mode
  - Needle component replaceable and supplied by end user
- **Auto-injectors**
  - Spring loaded
  - Uses energy source
  - Automatic mode
  - Needle tip shielded
  - Passive safety mechanism

Who is the Lead?

- Primary mode of action (PMOA)
  - Device PMOA = Center for Devices and Radiological Health (CDRH)
  - Drug PMOA = CDER

CDER-led Combination Products

- Task assignment to OGD Division of Clinical Review (CDER)
  - Comparative Analysis
- Intercenter Consult Request (ICCR) to CDRH
  - Engineering Device Design (OPQ/Drug Product Reviewer)
  - Facilities/Manufacturing Assessment (OPQ/Facility Reviewer)

ICCR to CDRH

CDRH review will not cover:

- Drug/Device (material) compatibility
- Sterility (primary container closure)
- Device user interface

ICCR to CDRH

CDRH review will cover

- Device performance
- Biocompatibility of patient contacting components or materials that are not drug contacting (will not review pre-filled cartridges and *staked in* needles).
- Device performance on stability
- Essential Performance Requirements (EPRs) Control strategy
- Quality Systems Assessment

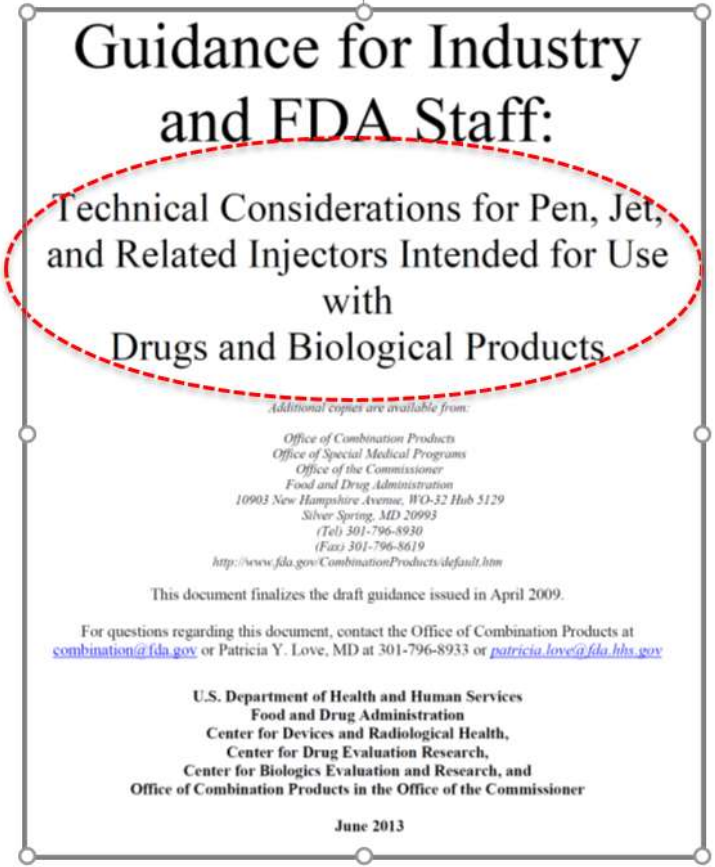
Shelf-life and Expiration Dating

- Provide stability data for three lots of **fully assembled and packaged injector-drug product**
- Assess shelf life of the assembled product in storage conditions before use
- Assess stability and expiration dating of the final to-be-marketed configuration under expected in-use conditions (e.g., rugged use, different environmental conditions)

EPR Examples (Auto-injector)

- Delivered volume accuracy
- Activation force
- Injection time
- Extended needle length
- Cap removal (emergency use)

Device Considerations



Guidance for Industry and FDA Staff:

Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products

Additional copies are available from:

Office of Combination Products
Office of Special Medical Programs
Office of the Commissioner
Food and Drug Administration
10903 New Hampshire Avenue, WO-32 Hub 5129
Silver Spring, MD 20993
(Tel) 301-796-8930
(Fax) 301-796-8619
http://www.fda.gov/CombinationProducts/default.htm

This document finalizes the draft guidance issued in April 2009.

For questions regarding this document, contact the Office of Combination Products at combination@fda.gov or Patricia Y. Love, MD at 301-796-8933 or patricia.love@fda.hhs.gov

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health,
Center for Drug Evaluation Research,
Center for Biologics Evaluation and Research, and
Office of Combination Products in the Office of the Commissioner

June 2013

Questions to CDER

- Stability orientation
- Number of Active Pharmaceutical Ingredient (API) lots and primary batches
- Lots of packaging materials
- Packaging of primary batches

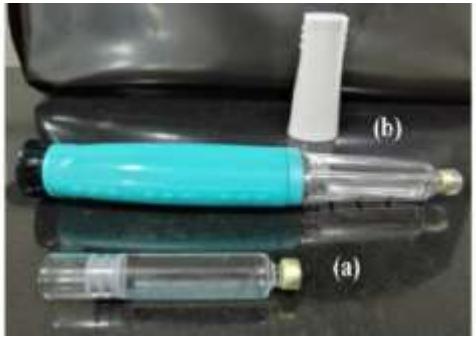
Stability Orientation

- Guidance for Industry *ANDAs: Stability Testing of Drug Substances and Products – Questions and Answers* (May 2014)
  - For primary batches of liquids, solutions, semi-solids, and suspensions, the product should be placed into an inverted (or horizontal) position and an upright (or vertical) position. For routine stability studies, the applicant should pick the worst case orientation for the study

Stability Orientation

- Guidance for Industry *ANDA Submissions – Refuse-to-Receive Standards Guidance for Industry* (December 2016)
  - FDA will Refuse to Receive (RTR) an ANDA if both worst-case scenario and non-worst-case stability data adhering to the recommendations described in section V.B.1 and this section (V.B.2) are not submitted for the described drug product batches: liquids, solutions, semi-solids, and suspensions

Case Studies – Stability Orientation



Filled cartridge (a)
Filled cartridge in pen (b)

Number of API Lots

- Guidance for Industry *ANDAs: Stability Testing of Drug Substances and Products – Questions and Answers* (May 2014)
  - A minimum of two lots of the drug substance should be used to prepare the three primary batches of drug product

Lots of Packaging Materials

- Guidance for Industry *ANDAs: Stability Testing of Drug Substances and Products – Questions and Answers* (May 2014)
  - Not necessary to use different lots of packaging material, except in cases where the packaging material could affect drug product quality performance (separate from CDRH's device performance stability requirements)

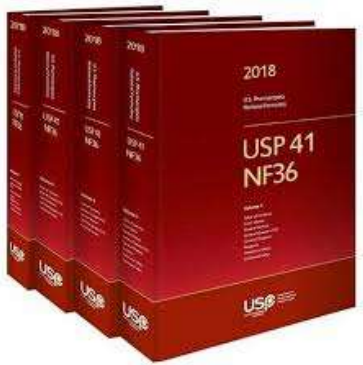
Packaging of Primary Batches

- Guidance for Industry *ANDAs: Stability Testing of Drug Substances and Products* (June 2013)
  - One primary batch using a full manufacturing assembly run. A subset of that batch will be put on stability for DP quality and Device performance stability studies.
  - Other two batches may be* partial manufacturing assembly runs that produce sufficient final finished products to fulfill DP quality and device performance stability studies

*dependent on manufacturing process (automated vs. manual) and control strategy

Drug Product Quality Attributes

- Particulate matter, USP <788>
- Visible particulate, USP <790>
- Volume in container, USP <697>
  - Overfill, USP <1151>
- Packaging Systems, primary



USP <1>
Universal Tests
Specific Tests

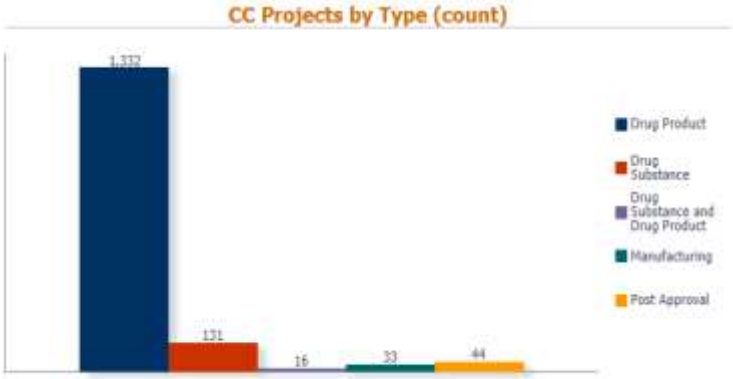
Primary Container Closure System

- Guidance for Industry *Container Closure Systems for Packaging Human Drugs and Biologics* (May 1999)
  - Qualification and Testing
  - USP chapters: <660>, <661>, <381>, <87>, <88>

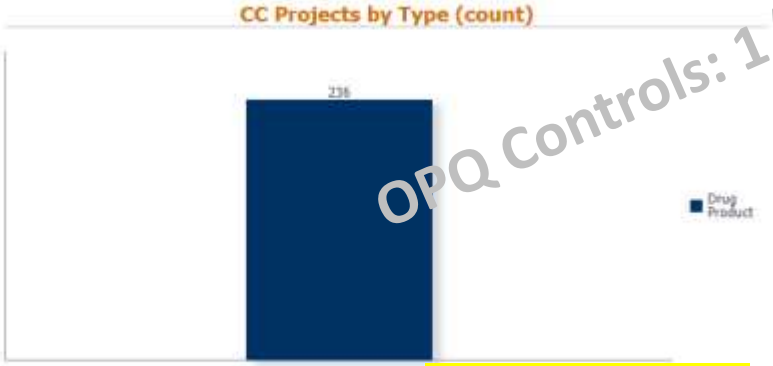
How to Connect?

- Guidance for Industry *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA* (October 2017)

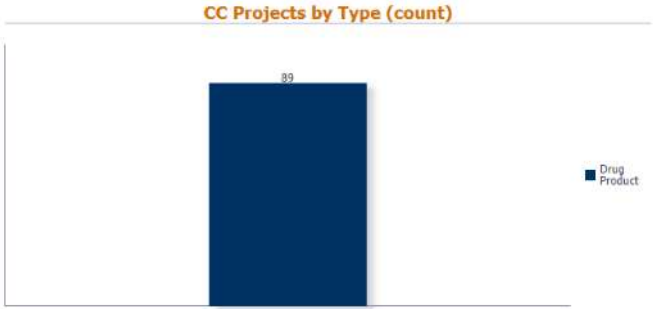
- Guidance for Industry *Controlled Correspondence Related to Generic Drug Development* (September 2015)



DP/Device



DP/Batch #/Batch Size



DP/Orientation/Stability Data Amount

OPQ Controls: 1/1/2016 – 8/17/2019

Summary

- Understand your product
- Know your resources
- Get product specific advice

- Efficient drug product development
- Facilitates application review
- Provides confidence in quality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