Guidance for Industry and FDA Staff:

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

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

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Contains Nonbinding Recommendations

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Guidance for Industry and FDA Staff[1]

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This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

Introduction

FDA is issuing this guidance document to describe the technical and scientific information that FDA expects in a marketing application for a pen, jet, or related injector device that is intended to be used with a drug or biological product.[2]

For purposes of this guidance, the term injector includes, but is not limited to: jet injectors, pen injectors, piston syringes, needle-free injectors, mechanically operated injectors, and injectors with computerized or electronic elements.

Pen, jet and related injectors may be marketed under different provisions. For example, pen injectors for general use are regulated as class II devices under 21 CFR 880.5860 (product code NSC) or 21 CFR 880.6920 (product code KZH).[3] Jet injectors for general use, including needle or needle-free injectors, are regulated as class II devices under 21 CFR 880.5430 (product code KZE). Typically such general use injectors are regulated by CDRH. When injectors are combined with, packaged with, or labeled for use with a specific drug/biological product they may be combination products.[4]

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[1] This guidance was prepared by the Office of Combination Products in the Office of the Commissioner in conjunction with the Center for Devices and Radiological Health, the Center for Drug Evaluation and Research, and the Center for Biologics Evaluation and Research.

[2] Throughout this guidance, we use the terms "marketing application" and "submission" interchangeably to reference whichever type may be appropriate for your product. The marketing application includes original submissions, amendments, and supplements, as appropriate.

[3] In identifying pen injectors, FDA distinguishes pen injectors from piston syringes and pen injectors with manually-inserted needles from pen injectors with automatically-inserted needles.

[4] Combination products are defined at 21 CFR 3.2(e).

This guidance does not apply to devices the sole purpose of which is to aid in the insertion of a syringe (product code IQG under 21 CFR 890.5050) nor to infusion sets (product code FPA under 21 CFR 880.5440). Also, this guidance does not apply to dental surgery gas-powered jet injectors (product code EGQ under 21 CFR 872.4465) or dental surgery spring-powered jet injectors (product code EGM under 21 CFR 872.4475).

This guidance supplements other FDA guidance documents that may apply regarding specific content requirements of a marketing application and any electronic and software components of your product. See Section III for a list of some additional guidance documents that may be useful when developing pen, jet, or related injectors for use with drugs and biological products.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Background

Pen, jet, and related injectors may provide an innovative approach to deliver drugs or biological products, and they may enhance safety, improve dosing accuracy, and increase patient compliance, particularly in self-administration settings. For example, these injectors are designed to provide an accurate method of injecting a dose of drug/biological product contained in a cartridge, reservoir, or syringe through an automatically or manually inserted hypodermic needle(s) or through a high velocity jet. They are intended for use by a healthcare provider or for self-administration by a patient. Injectors may be designed for single use or multiple uses, and may be disposable or reusable. For example, a single use injector may be used in acute intervention for treatment or prevention while a multi-dose injector may be used as part of a single patient long term treatment regimen.

There are three basic usage groups of injectors. First, there are general injectors intended for use with a wide range of drugs/biological products. Second, there are injectors intended for use with a certain class/family of drugs or biological products, or with a specific product line.[5] Third, there are injectors intended for use with a specific drug/biological product; e.g., a) pre-filled with the drug/biological product, b) co-packaged with the drug/biological product, or c) separately distributed but labeled for use together.

[5] For purposes of this guidance document, "class" and "family" are used interchangeably. An example of an injector to be used with a "class or family of product" is an injector designed for insulin drug formulations. An example of an injector to be used with a "product line" is an injector intended to be used with all injectable products that a specific company markets.

Injectors are subject to different regulatory requirements depending, for example, on their intended use, technological characteristics, proposed labeling, and packaging. For instance, as noted above, injectors intended for general use with a wide range of legally marketed drugs/biological products (i.e., without a specified drug or biological product) generally are regulated as class II medical devices under the premarket notification (510(k)) provision. Likewise, injectors intended for use with a certain class/family of drugs/biological products often are regulated as class II medical devices under the 510(k) provision. Injectors intended for use with a specific drug/biological product are typically considered combination products under 21 CFR 3.2(e).[6] Combination product assignment is based on primary mode of action (PMOA).[7] Combination products with a drug or biological product PMOA are assigned to CDER or CBER for regulation. For combination products comprising an injector and a drug/biological product, one marketing application is generally sufficient; this application is usually an NDA or a BLA.[8]

This guidance focuses on the scientific and technical considerations that a manufacturer should consider when developing a pen, jet, or related injector and submitting a marketing application. It provides considerations applicable to all injectors described above. It also provides general content and format information for injectors that are reviewed under 510(k) submissions as well as injectors reviewed under an NDA or BLA submission for the combination product.

SECTION I: SCIENTIFIC AND TECHNICAL CONSIDERATIONS FOR YOUR PREMARKET SUBMISSION

A. Injector Description

Given the spectrum of injector designs, we recommend that your premarket submission includes a comprehensive description of your product, its indication(s) for use, and its conditions of use. Depending on the product, the submission should include the following elements, as applicable:

1. Identification

The proposed injector should be identified using the following information:

- Trade name or proprietary name of the injector
- Associated name; e.g., generic or other name of the injector[9]

[6] General information on combination products is available at http://www.fda.gov/CombinationProducts/default.htm.
[7] Combination products are assigned to a Center for primary review and regulation based on a determination of the product's primary mode of action (PMOA); 21 CFR 3.4.
[8] Please see section I.A.4, below, for general information related to the marketing application.
[9] In a 510(k), a classification name relates to the injector characteristics. 21 CFR 807.3(j).

- Device classification regulation (e.g., 21 CFR 880.5860) and product code (e.g., NSC).[10]

2. Indication For Use

The proposed indication statement should include the following items:

- Patient population (e.g., medical disorder, demographics)
- Injection site (area on the body where the drug/biological product is injected)
- Intended injection tissue and depth of injection (e.g., subcutaneous, intramuscular, intradermal)
- Type-of-use (e.g., individual patient use as a single, disposable, reusable, or refillable injector)
- Purpose of product use (e.g., for general use or for use with a product class, family, product line, or a specifically named drug or biological product)
- Intended user (e.g., patient, caregiver, health care provider)

The following table illustrates some of this information.

Type of Use	Description
Single-use	Entire injector and primary container closure or drug container is discarded after a single use
Disposable	Injector can be used more than once for a single patient only with the same primary container closure or drug container in place and is discarded after the drug container is empty
Reusable	Injector can be used more than once for a specified single patient only with replaceable primary container closure or drug container
Other	Describe any unique type-of-use or intended user conditions;
Intended User	**Description**
Personal	For self-administration or by a caregiver
Professional	For use by a healthcare provider in a healthcare or institutional setting for a specified single patient only

[10] The device classification and code only apply for injectors submitted under a 510(k).

3. Description of Conditions of Use[11]

The discussion of the conditions of use for the injector should include:

- Method of injection (e.g., manual piston, spring load, gas, jet, other)
- Drug/biological product(s) intended for delivery by the injector
- Dose capability (e.g., single dose, multiple dose, adjustable dose)
- Packaging configuration (e.g., as a pre-filled injector-drug/biological product, as a co-package containing the injector and drug/biological product for assembly, or as a separately distributed injector)
- Environment of use conditions (e.g., home, school, battlefield)
- Storage, handling, and other use factors for pre-filled injectors; e.g., refrigeration, environmental conditions and/or protection from light, and warming to room temperature before injector actuation.

4. Description of Drug/Biological Product for Injection

As noted above, there are three different usage groups of injectors: (a) injectors intended for use with a wide range of legally marketed drugs/biological products (general use), (b) injectors intended for use with a specific class or product-line of legally marketed drugs/biological products, and (c) injectors intended for use with only a specific drug/biological product. Overall, the descriptive information on the drug/biological product should reflect the following considerations as applicable to each injector configuration and the drug/biological product intended for injection:

a) General use injectors: Typically, general use injectors are regulated under the 510(k) premarket notification process. In order for FDA to clear a general use injector for marketing, at least one injectable product (e.g., a drug or biologic) must already be approved for use in the dose, rate, route, configuration, and the method of injection submitted in the 510(k)).[12] For general use injectors, the description section of your application should include the following information, in addition to the information recommended by other applicable guidance.

   - The name(s) of the drugs/biologic products that are currently approved and marketed for the dose, rate, route, and method of injection proposed for the general use injector. Your submission should include

[11] Information in the "Conditions of Use" section may also be part of the "Labeling Indications," the "Use and Handling," or the "Dosage and Administration" section, as appropriate depending on the type of marketing application submitted (e.g., Structured Product Labeling in an NDA/BLA – see Guidance for Industry, Indexing Structured Product Labeling assessable at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072317.pdf).

[12] In cases where only one marketed injectable product is available or, if a compatible drug/biological product or configuration is in development or pending approval, or if there are drug/biological product-injector compatibility concerns; FDA recommends that you contact the CDRH review branch or the Office of Combination Products to discuss whether general use is appropriate.

a copy of the most recent labeling for the representative product(s) of the range of approved drug/biological products that are currently marketed to be used with your injector. Specifically, for each injectable product and its approved diluent for use in reconstitution, the submission should include a copy of the approved labeling of the diluent and the approved labeling of the drug/biological product proposed for reconstitution. The approved labeling of the drug/biological product should indicate that the product is approved for the dose, rate, route, and using the method of injection of the proposed injector. The dose is generally identified as a concentration or volume. The route of injection includes, subcutaneous, intradermal, intramuscular, or intravenous. The rate reflects differences in flow rate produced by a manual piston syringe, power, jet or other forces.[13]

- The characteristics and composition of the drug/biological product that are compatible and not compatible with your injector material and performance characteristics. FDA uses this information in part to inform final device labeling language. If identifying incompatible drug/biological product characteristics is not feasible, then provide a scientific rationale for why the characteristics were not tested. Examples of composition considerations include active and inactive ingredients, pH, viscosity, preservatives, and osmolarity along with the aqueous or oil-based characteristics. If you are considering submitting representative product data for a general use injector (instead of testing with specific drugs or biologic products), contact CDRH for discussion on whether such representative testing is appropriate for your submission. (For additional information on performance testing for general use injectors, see Section I.D.)

b) Injectors intended for use with a class/family of products, with a specific product line, or with a specific drug/biological product: If the injector is intended to deliver a specific drug/biological product, a certain product line, or a class/family of products,[14] your submission should include the following.

- The approved product(s) for injection by brand and/or generic name and their labeled indication(s) for administration. In these circumstances, FDA intends to consider whether the target product, product line, or class/family of products is currently approved for the dose, rate, route, and using the method of injection proposed for the injector. We also recommend that your submission includes a copy of the most recent product labeling of the approved drug/biological product(s) in the family/class to be used with your injector. For some

[13] Generally when the rate or method of injection is not specifically identified in the drug or biological product labeling instructions or clinical trials section, the default method is that of a manual piston syringe.
[14] See footnote 5.

very narrow product lines with consistent product characteristics, it may be acceptable to provide a copy of the labeling for one representative drug or biological product within the product line. (For additional information on performance testing for these products, see Section I.E. For additional information on labeling, see Section I.H.)

- Documentation that the drug/biological product is currently approved for marketing in the necessary configuration for use in the injector.

If you are proposing your injector for use with an unapproved drug or biological product, or for use with an approved drug or biological product but using a new route, dose, rate or method of injection, the relevant Centers will identify the necessary data for the premarket review of the drug/biological product, and the appropriate type of submission(s) for the unapproved product(s) and the injector.[15] We recommend that you contact the Office of Combination Products for additional information to determine the lead center.[16]

If you are providing injectors to pharmaceutical firms (or entities such as holders of other marketing applications) for further manufacturing, pre-filling, or co-packaging, and if you wish to maintain certain confidential information regarding your injector, you can provide FDA with proprietary information about these injectors in a device master file submission to CDRH. When doing so, you should also provide letters of authorization to the other firms/application holders who are performing the additional manufacturing steps or are relying on your information.[17] These other entities could then reference the information in your device master file when they provide their own marketing submissions (i.e., NDA/BLA). For pre-filled injectors and for injectors co-packaged with a drug/biological product, the marketing application should identify which application holder/manufacturer/supplier will perform the pre-filling, co-packaging, and other manufacturing steps to produce the final finished product for marketing. For additional procedural information see Section III.

B. Design Features

Design features encompass the technical specifications of the injector, the characteristics of the injectable product, the injector configuration (e.g., general use, prefilled, or co-packaged) and the human factors to be considered to ensure safe and effective use of the product. When submitting a general use device under 510(k), the design information in section I.B.1-6 below should be compared to the predicate device.

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[15] Changes in the dose, rate route or method of injection may trigger the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c). See FDA Guidance *How to Comply with the Pediatric Research Equity Act* ; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079756.pdf.

[16] See http://www.fda.gov/CombinationProducts/default.htm and footnote 7.

[17] For more information on medical device master files (MAFs) and authorized references see http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/ucm142714.htm.

1. Comparison to an Existing Delivery Method

To facilitate the regulatory review of the injector, manufacturers may compare various design features of their injector to features in similar legally marketed products. The goal of this comparison differs depending on the injector use and regulatory pathway for the injector.

a) General use injectors (510(k) pathway):

The 510(k) marketing pathway requires demonstration of substantial equivalence to a legally marketed predicate injector(s).[18] The following are examples of comparative information that you should provide in a 510(k) submission. For additional information also see Section I.D., Performance Testing.

- 510(k) number(s) of the predicate(s)
- Indications for use of the new injector
- Conditions of use
- Injection sites
- Where applicable, depth of needle insertion for route of injection
- Injector life
- Compatible cartridges
- Where applicable, compatible needles
- Dose, dose accuracy, rate of injection, frequency of injection, and precision (including mechanisms to determine the dose)
- Power source
- Overall dimensions
- Weight
- Design features
- Materials of construction
- Performance specifications and profile (e.g., force, pressure)
- Where applicable, needle lumen and jet injector nozzle orifice size
- Drug/biological product(s) intended for use with the injector

b) Prefilled injectors, injectors co-packaged with the drug/biologic, or injectors and drug/biologic distributed separately and marketed under the NDA/BLA pathway:

For prefilled injectors, co-packaged injectors, or injectors and drug/biologic distributed separately and marketed under the NDA/BLA, each premarket submission is reviewed and approved for a specific injector with a specific drug/biological product. In most instances, data required in a general use injector 510(k) are not sufficient to address the safety or effectiveness questions for

[18] See 21 CFR Part 807 Subpart E.

the device constituent part of a combination product submitted in the NDA/BLA (i.e., to demonstrate safe and effective use with a specific drug/biological product for the combination product indication). For example, a general use 510(k) does not contain specific safety and effectiveness information on the dedicated drug-injector combination, its specific characteristics, or the intended patient population. Therefore, the submission should include injector-drug/biological product specific data. In addition, if the injector for the drug/biological product would change, for example, the route or method of injection, or other characteristics of the approved drug/biological product, then the NDA/BLA should include the relevant data (e.g., pharmacokinetics or other end-points from oral, intravenous, intramuscular, or subcutaneous dosing) in comparison to other approved drug/biological product delivery methods as appropriate. Also see section I.D.

2. Engineering Drawings and Photographs

We recommend that you provide engineering component and assembly drawings for your injector which includes the following key functional components:

- Fluid path and reservoir
- Power supply
- Dose-setting mechanism, such as a dial, used to set the desired dose

In addition, you should provide the following:

- Exploded views and photographs of the injector and illustrations showing the drug product delivery stages
- Engineering drawings with critical dimensions and tolerances
- List of the components incorporated in the injector

3. Dose Setting and Administering an Injection

In order for FDA to assess the ability of the injector to reliably and reproducibly deliver the desired injection volume of the target drug/biological product(s) into the target tissue, and to compare the reliability and reproducibility to those of the predicate injector (or other delivery method as appropriate), we recommend you provide a description of the procedures for setting and administering the drug/biological dose when using the new and predicate injector including (if applicable):

- Assembling the injector at the point of clinical use
- Loading the drug/biological product
- Priming the injector
- Pre-setting the dose
- Inspecting the drug/biological product
- Preparing and positioning for an injection

- Adjusting the dose
- Resetting after use
- Changing and disposing the needle

Likewise, we also recommend that you include, if applicable:

- A description of the power source for the injector.
- A description of the controls, such as dose indicators, activation status, and reservoir volume.
- The method and mechanism for ensuring that the drug/biological product in the chamber or cartridge is sufficient for the desired volume of delivery.
- A discussion of the frequency of incomplete or partial dosing, or overdosing events, and the actions necessary to remedy these events.
- The time required for delivery of the drug/biological product.
- If the injector has a retractable fixed needle, a discussion of how the design ensures that the full dose will be delivered prior to needle retraction.
- For jet injectors, a description of the nozzle design (e.g., single orifice, multiple nozzles/orifices of different sizes).
- A description of all of the attachments that are necessary for the proper operation of the jet injector, even if they are not part of the injector proposed for marketing, or part of a cleared or approved product being referenced (e.g., a regulator for compressed air, transfer device, IV luer lock needleless connector, needle, and/or needle array).
- If assembly by the user is required, a detail description of how the injector is assembled; if the injector is pre-filled, a detail description of how the drug/biological product is contained in the injector.

4. Graduation Marks and Fill Lines

Graduation marks and fill lines may be used to aid the user in setting the correct dose or for verifying the set dose. We recommend that these markings be included in the design of the injector to aid proper dosing in accordance with the approved drug/biological product labeling, when:

- The injector is intended to deliver multiple doses of a drug/biological product;
- The dose can be adjusted by the user; or
- The injector is intended to deliver a single dose of a specific drug/biological product and the risks associated with under- or over-dosing are critical as determined by a risk analysis.

When using graduation marks or fill lines, the submission should include validation of the accuracy of these markings. If graduation marks/fill lines are not feasible, then the submission should provide an alternative method to alert the user if under or over-dosing occurs.

5. Visual Inspection of the Drug/Biological Product

In some circumstances, the drug/biological product for delivery has labeling instructions requiring visual inspection of the product before injection. (In part this ensures compliance with the 21 CFR 201.57(c)(3)(iv) requirement for the Dosage and Administration labeling section to include the following verbatim statement for parenterals: "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.") As a result, the injector design should allow for appropriate inspection. For example, for a pre-filled injector that holds a cartridge for future or repeat dose use that cannot be removed once it is placed in the injector, the injector design should permit the appropriate visualization of the drug/biological product when it is in the injector. Additionally, the inspection should allow the visualization of the drug/biologic name and concentration/strength in order to minimize medication errors.

6. Safety Features

Injectors may have a variety of safety features to ensure accurate dosing and to prevent sharps injury. In addition to graduation/fill marks and visual inspection, these features may include audible, visual, and tactile notifications as well as switches and mechanical protections. We recommend that you describe all safety features of the injector including alarms, warnings, and switches, their purposes, and their instructions for use, and provide testing to demonstrate that the safety features perform as intended. If the injector has a sharps injury prevention feature (e.g., retractable needle), we recommend that you address the issues discussed in the guidance document *Supplementary Guidance on Premarket Notifications for Medical Devices with Sharps Injury Prevention Features* (Aug. 2005), available at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071663.htm. See also FDA 2011 communication on "*Needles and Other Sharps - Safe Disposal of Sharps Outside of Health Care Settings*" at http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/HomeHealthandConsumer/ConsumerProducts/Sharps/default.htm.

We also recommend that you conduct a risk analysis that considers the overall product and includes both the injector and drug/biological product for injection. Specifically, you should assess the risk of use of the intended drugs/biological products delivered with the injector as related to the human factors characteristics of the patient population using the intended drugs/biological products. For additional discussion on human factors see Section I.B.7 below and Section I.F.)

7. Human Factors Design Considerations

The design of the injector should take into consideration the intended user population, the expected indications for use, and the environment of use. For example, in home use populations, these factors should include age, tissue characteristics at site of

injection, and any limitations in the perception, strength, mobility, and manual dexterity among the user population for whom the injector is intended.[19] Injectors that are designed for user populations that might have visual impairments or manual dexterity limitations might need to have design features that accommodate those limitations; e.g., auditory alerts, larger easy grip. Likewise, injectors intended for use by individuals serving in the military should take into account the wide range of environmental conditions under which the injectors will be stored and possibly used (e.g., in desert or tropical climates or frigid conditions, and at various altitudes, such as in an aircraft or in a submarine). Other factors associated with the environmental conditions include ambient lighting, noise, and user physical activity levels. Careful evaluation of how these factors can affect safe and effective use of the injector, and how they can be mitigated should be assessed during the design and development of the injector. (See Section I.F for further discussion of human factors).

C. Materials Used in Injector Construction and Manufacture

Your marketing application should identify all known materials that comprise the injector as well as the manufacturing materials used in construction of the injector. For general use injectors submitted under a 510(k), for each component of the injector, please specify the nature and composition of all materials of construction and identify any differences in comparison to the predicate. The submission should provide the chemical, grade, and brand name, and indicate which materials are in or will affect the fluid path.[20] It should also identify any components or materials that are not identical to those of the predicate injector (e.g., plastic stoppers instead of rubber stoppers). For any new component or materials of construction, the submission should include the methods and results of testing described in this section. Also, the submission should include a comparison of the characteristics of the drug/biological products intended for use with the predicate injector versus the drug/biological products intended for use with your proposed injector.

Certain drugs/biological products have different responses to metals and manufacturing materials that may be components of an injector (e.g., silica, steel, carbon, polymers). Also, some drug or biological products may interact with manufacturing process residuals. The submission should, therefore, include the results of tests that examine the interaction between the injector materials of construction, manufacture, and process residuals with the drug/biological product. These tests should evaluate how the injector-drug/biological product interactions affect each other's performance. The testing should include the entire product use cycle functionality testing in the stability program (see Section I.D.2 and I.D.3).

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[19] See *Draft Guidance for Industry and FDA Staff - Apply Human Factors and Usability Engineering to Optimize Medical Device Design* (June 2011), available at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm. When finalized, this guidance will represent the FDA's current thinking on this topic.

[20] For purposes of this guidance, materials that are in or will affect the fluid path are components and accessories of the injector that make contact with the drug/biological product, including the needle, dose chamber, cartridge, plungers and stoppers, and reservoirs for the drug/biological product.

Testing should characterize the components of the injector, the component materials, and residuals from the manufacturing process. For injectors submitted under the NDA/BLA the same information should be submitted, but the comparison to a predicate is not applicable. The following list describes specific issues FDA intends to consider in reviewing the submission:

- Analysis of leachables arising from the interaction between the drug/biological product and injector (see Section 1.E.3)
- Analysis of extractables from the injector components using solvents under laboratory conditions and providing the extraction profiles (see Section 1.E.3)
- Analysis of adsorption of drugs/biological products (including preservatives) onto injector components
- Analysis of head-space volatile compounds when the injector is the primary containment closure for the drug/biologic
- Analysis of drug-injector interaction over time for re-useable injectors
- Analysis of functional materials corrosion from contact with the drug/biologic product.
- Analysis of seal integrity (e.g., lubricity breach of sealing)
- Identification and analysis of effect of introduced particulates

D. Performance Testing: General Use Injector Considerations

Performance testing for general use injectors should be with the final injector for marketing and should take into account the characteristics of the wide range of drugs/biological products in their final approved dosing form (including their approved diluent for reconstitution) with which your injector is intended to be used. Also, as appropriate for the injector design, the testing should demonstrate the drug/biological product composition characteristics that are compatible with the injector and those that are not (see Section I.A.4.a). FDA recognizes that in some general use circumstances, it may be acceptable to conduct testing with a range of representative drug/biological products. If such testing is proposed, the submission should provide a detailed justification for why it is appropriate and why the chosen product or range of products is acceptable. When conducting performance testing, we recommend that you follow the most current version of the standards recognized by FDA which are identified below and at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm.[21]

- ISO 7886-1: *Sterile Hypodermic Syringes for Single Use - Part 1: Syringes for Manual Use*
- ISO 10993-1:*Biological Evaluation of Medical Devices - Part 1: Evaluation and Testing*
- ISO 11608-1:, *Pen-Injectors for Medical Use – Part 1: Pen-injectors – Requirements and test methods*

[21] In a 510(k) submission when the data comply with FDA recognized standards, the submission may include summary data. However, full data should be available to provide upon FDA request during review process. Standards documents are available from the authorizing organizations.

- ISO 11608-2: *Pen-Injectors for Medical Use – Part 2: Needles – Requirements and test methods*
- ISO 11608-3: *Pen-Injectors for Medical Use – Part 3: Finished Cartridge – Requirements and test methods*
- ISO 11608-4: *Pen-Injectors for Medical Use – Part 4: Requirements and test methods for electronic and electromechanical pen-injectors*
- ISO 21649: *Needle-Free Injectors for Medical Use - Requirements and Test Methods.*
- ASTM D4169:, *Standard Practice for Performance Testing of Shipping Containers and Systems*

If applicable, FDA also recommends that you conduct software, electrical safety, and electromagnetic compatibility testing for your injector. Guidance on testing these aspects of your injector is available from FDA.[22]

FDA recommends that your submission include results from the performance testing on the finished products as follows:

- List the specific bench tests conducted
- Description of each test protocol
- Summary of the results
- Description of your analysis, and
- Discussion of your conclusions

The description of test protocols should identify the:

- Objective of the test
- Test articles used in the test
- Test methods and procedures (including any specific test conditions)
- Study endpoint; i.e., the specific parameter measured, and
- Pre-defined acceptance or pass/fail criteria.
- Test procedures to demonstrate that the injector connections are compatible with other devices necessary for use but are not part of the submission (e.g., transfer device, IV luer lock needleless connection, needle, needle array).[23]

1. Biocompatibility

For general use injectors, FDA recommends that you conduct biocompatibility testing as described in the guidance, *Use of International Standard ISO-10993, Biological*

[22] See *General Principles of Software Validation; Final Guidance for Industry and FDA Staff* (Jan. 2002); http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm085281.htm.

[23] For examples of connectivity concerns, see FDA Safety Communication: Needleless Pre-filled Glass Syringes: Stakeholder Advisory - Compatibility Problems with Needleless Intravenous Access Systems; http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm234219.htm. Also, see FDA Drug Safety Communication: Connection problems involving certain needleless pre-filled glass syringes containing adenosine and amiodarone; http://www.fda.gov/Drugs/DrugSafety/ucm254215.htm.

Evaluation of Medical Devices Part-1: Evaluation and Testing.[24] The biocompatibility testing should consider components or materials in contact with the patient, including components or materials that are in the fluid path that externally communicates with the patient's body (e.g., skin, tissue, blood, bodily fluids). The selected biocompatibility tests should be appropriate for the type and duration of contact with your device. Summaries of biocompatibility testing should include:

- Listing of the specific tests you conducted
- The details of extraction testing (e.g., whether the entire injector or only a small piece of the injector was extracted, whether all the components were included in the extraction, whether the extraction was performed on the finished injector subject to all processing methods and sterilization)
- The extracts tested and justification for the choice of extracts (e.g., polar, non-polar)
- The animal model or cell line
- The extract conditions (e.g., time, temperature, area- or mass-to-volume ratio compared to in-use conditions)
- The test and controls used
- The end points used
- As appropriate, toxicity testing of extracts described in the United States Pharmacopeia USP<87>, USP<88>, USP<381> and USP<661> as well as systemic toxicity, delayed dermal contact sensitization studies, non-pyrogenicity testing, cytotoxicity testing using red blood cells and mouse fibroblasts, and Ames assays.[25]

Depending on the specific materials in the product and conditions of use, FDA may request additional pharmacology-toxicology testing.

2. Shelf-Life Stability and Expiration Dating

For stability and expiration dating, the testing should consider the general use injector's shelf-life/expiration dating before it is actually used and the injector in-use life with the drug/biological product. The test data should include a demonstration that at the labeled expiration date the injector can still be reliably and reproducibly used for the labeled number of injections with the same dose accuracy. FDA recommends that shelf and in-use life-testing endpoints include:

- Freedom from defects (e.g., displaced parts, cracking, leaking, change in injection force)
- Proper assembly of replacement needles and cartridges
- Accuracy of delivered dose (see Section I.E.1)

[24] *ISO-10993, Biological Evaluation of Medical Devices Part-1: Evaluation and Testing* http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080735.htm.
[25] United States Pharmacopeia information is accessible at http://www.usp.org.

As above, the submission should include an analysis and discussion of the physical degradation of and changes to the injector before use and during use due to the exposure conditions. For additional information relating to the life of an injector, see Section I.E.2.

3. Environmental Conditions

You should submit data to verify that the injector performance is not adversely affected by environmental conditions, such as the following:

- Sterilization
- Extreme operating temperature environments (i.e., upper and lower ends of the specification)
- Extreme storage temperature environments (i.e., upper and lower ends of the specification)
- Extreme conditions of use testing, when applicable (i.e., upper and lower ends of the specification)
- Packaging
- Shipping conditions

In addition, for jet injectors, the extent of "wear and tear" on the nozzle and fluid path is of concern. The high jet stream velocity and pressure may have deleterious effects on the fluid path and the nozzle, including erosion, component deformation, and structural failure. These effects should be assessed in relationship to the injector and component service life, servicing, or replacement intervals.

4. Functional Testing

Depending on the type of injector, as appropriate for the injector design, a company may be asked to conduct additional bench testing to demonstrate that the injector functions as intended. Testing to assess the functionality of your injector may include:

- Flow rate
- Injection time (i.e., time required to deliver the drug/biological product)
- Reliability of the mechanism to deliver the drug/biological product
- Depth of injection
- Safety features
- Verification for absence of leakage
- Verification of non-coring needle (e.g., if the needle is used to puncture a septum)
- Needle dwell time (i.e., amount of time that the needle is in the body)
- Chemical resistance (i.e., data to ensure that the injector and its label are not adversely affected by the recommended cleaning agents)
- Structural testing at extreme pressure and temperature conditions

Testing to assess the mechanical specifications of your injector may include:

- 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 (i.e., force required to pull the needle off the injector)
- Needle penetration force (i.e., force available for needle insertion)
- Needle deflection angle that causes injector failure (note: this is important if the needle retracts after insertion)

The above tests should include testing of all safety features to ensure they perform as intended. Also, for multiple use injectors, the testing should verify the duration of repeated use.

E. Performance Testing: Injector and Drug/Biological Product Considerations

For a general use injector, in association with the considerations in Section I.D, the submission should include the results from performance testing of the final finished injector for final finished dosage form for testing of the drug/biological product dose accuracy and for depth and route of injection as described below. For injectors intended for use with a certain class/family or product line or with a specific drug/biological product, when developing your plan for performance testing you should begin with the considerations described in Section I.D and should then focus on the unique attributes of the injectable product class/family or product line, as described below. Likewise, subsequent to the applicable considerations in section I.D, the following testing considerations apply to the specific drug/biological product of a combination product.

When conducting performance testing for your injectable product, you should use the actual drug/biological product(s) in its final approved dosage form (including its approved diluent, if applicable) as intended for injection. For example, for an injector intended for use with a specific drug, you should perform biocompatibility testing with that drug (see Section I.D.1).

When conducting performance testing for a class/family or product line, you should consider the type of testing necessary to evaluate the expected injector-drug/biological product interactions. For example, if the injector materials are coated with a polymer, then the submission should identify which types of drug/biological product characteristics were tested to demonstrate an acceptable level of leachable or extractable material into the drug/biological product (see Section I.E.3 below).

We recommend that your submission include results from the following performance tests, in addition to the tests identified in Section I.D:

1. Dose Accuracy

Using your final injector, FDA recommends the following injection dose accuracy testing for the drug/biological product in its approved dosage form for injection, including the use of the approved diluent as applicable. If the study is for a device-drug/biological product pending approval, then the testing should use the final combination.

- Testing to demonstrate that the volume/weight of drug/biological product expelled through the injector is the same as the set dose
- Testing to ensure that multi-dose (fixed dose) cartridge injectors are designed to accurately deliver the fixed dose each time for the number of multi-dose injections specified in the labeling
- Testing to ensure that multi-dose (variable dose) cartridge injectors are designed to accurately deliver each successive randomly set dose
- Testing to ensure that dose settings/markings correlate with the volume of drug/biological product delivered

We recommend, where appropriate, that injectors include an alarm that notifies the user when only a partial dose has been delivered. Performance testing should include testing of such alarm(s). Product labeling should also include information instructing the user on what action should be taken in the event of partial dosage. (In addition, see information in Section I.B.4.)

2. Depth and Route of Injection

Testing should demonstrate that the depth of needle penetration and/or dispersion of the drug/biological product in the target tissue are accurate and consistent. The model chosen for this testing should be human skin and any specific tissue layers, or should simulate the human target tissue as closely as possible. If the selected model is a simulation of human tissue, the application should include an explanation to justify why the model is appropriate.[26]

Where applicable, provide a statistical comparison and justification for any differences between the measurements for the subject injector and those for predicate injectors or other delivery methods, as appropriate for the development question being addressed. (See section I.B.1)

Certain drugs or biological products require delivery to a precise tissue plane (e.g., intradermal, subcutaneous, intramuscular). Where applicable, the submission should include test results demonstrating reliable and reproducible depth of delivery (e.g., amount delivered subcutaneously, intradermally, or intramuscularly). Also see Section I.B.7 and I.F.1.

[26] Examples of acceptable depth of penetration testing include, but are not limited to, human, porcine, and cadaver models.

For injectors that involve the mechanical actuation and insertion of the hypodermic needle, jet injection or needleless injector, we recommend that you perform additional testing to examine the following parameters:

- Reliability for the specified depth of insertion throughout the expected injector life cycle
- Injector performance such as the amount of pressure needed to administer an injection and the permissible areas of body that may receive successful injections
- How population-specific issues, such as gender, body weight, age, and skin disorders, may affect injection safety or effectiveness
- The presence of blood vessels to avoid intravascular injection (if applicable)

For jet injectors, testing should also characterize the fluid dispersion from the injection to indicate the percentage of fluid in or at the surface of the muscle and at various depth ranges in the subcutaneous region. The submission should include images of injections depicting the distribution of the injected drug/biological product.

3. Special Testing Considerations

If the injector materials also comprise the container closure system for the specific drug/biological product, then you should perform the following in-vitro testing to support the performance of your injector with the specific drug/biological product. In some circumstances, similar testing may be appropriate for injectors intended for use with a class/family or product line.

- **Extractables or Leachables**

  In addition to the studies identified in Section I.C, you should provide studies that evaluate head space volatiles in the cartridge. Specifically, you should demonstrate that any seals or o-rings have the ability to contact different method of injection drug/biological products without sloughing or leaching material. Testing should also demonstrate seal integrity. Other testing that may be applicable to identify interaction with the injector and the injector manufacturing materials include:
  - Extractant analysis: e.g., pH shift, turbidity, heavy metals, non-volatile residue, residue on ignition, UV absorption, silicone content.
  - Chromatography: e.g., nucleating agents, cross-linking agents, curing agents, antioxidants, acid scavengers, plasticizers.
  - Impurities and degradation products
  - Endotoxins

In addition, data should include the methods and assay sensitivity used to determine the acceptable level of device materials leachable or extractable into the drug product.

- **Adsorpables**

Testing should evaluate the presence of drug/biological product or component gases, liquids, or solutes that accumulate on a surface of the injection device. Data should include the methods and assay sensitivity used to determine the acceptable level of drug/biological product adsorpables.

- **Drug/Biological Product Container and Closure Integrity**

For the configuration in which the injector or its fluid path is in direct contact with the drug/biological product, we recommend consideration of the principles in the FDA guidance, *Container Closure Systems for Packaging Human Drugs and Biologics: Chemistry, Manufacturing and Controls Documentation* (May 1999); available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070551.pdf.

- **Shelf-life and Expiration Dating: Injector-Drug/Biological Product**

Applications for injectors intended for use with a specific drug/biologic product or for a drug/biological class/family or product line should include stability data to establish the shelf-life and expiration dating of the relevant fully assembled injector-drug/biological product. For example, as appropriate, tests may assess the shelf life of the assembled product in storage conditions before use. They may also assess stability and expiration dating of the final to-be-marketed configuration under expected in-use conditions (e.g., rugged use, different environmental conditions). Where applicable, the tests should evaluate the product after reconstitution. They should assess any injectate that remains in the fluid path after injection; e.g., to determine if it degrades or contributes to the denaturing of the drug/biological product. As applicable, the in-use life testing should include data to demonstrate that the method of injection (e.g., rate, shear force, injection pressure) does not affect stability, safety, or effectiveness of the drug or biological product(s).
When conducting stability and expiration dating tests, the entire injector system should be tested; i.e., the drug/biological product in its direct container closure (cartridge) plus any surrounding injector materials and packaging. Bench testing for container closure and packaging ruggedness should include, but is not limited to, mechanical reliability (release specifications), accelerated testing, temperature cycling, temperature extremes, pressure changes, vibration, etc. (For information on testing of a general use injector, see Section I.D.2.)

F. Performance Testing: Clinical Considerations

Specific considerations for clinical trial design are beyond the scope of this guidance. Human factors studies would evaluate user interactions with the injector and whether the intended user population could safely and effectively use the injector with the specified drug/biological product.

1. Human Factors

To demonstrate that the users can safely and effectively use the injector in subsequent pivotal clinical studies, you should perform a comprehensive evaluation of all user related risks, and as needed, conduct human factors/usability studies with the final version of the device to validate users' performance with representative users. Depending upon the characteristics of the injector, its intended user population, and the environment of use, the studies should focus on essential aspects of using the product. These aspects may include, for example, the ability of users:

- To read, understand and follow instructions;
- To adequately set up the injector;
- To reconstitute injectable materials, draw up or set the proper dose, prime the injector (if required);
- To perform the injection or self-injection correctly; and
- To dispose of sharps and other disposable materials safely and properly.

2. Additional Considerations

FDA may request additional in-use information for critical features of injectors intended for use with a specific drug/biological product. For example, additional information may be appropriate for certain lock-out features, complex dose-adjustment methods, or other high-risk systems. For such products, we recommend that you contact the lead review division to discuss other pre-clinical and clinical data requirements.

G. Sterilization and Sterility Assurance

1. Sterilization

Sterilization incorporates two aspects: the sterility assurance necessary for the injector itself and the sterility assurance necessary for the final finished injector-drug/biological product as a whole. For general use injectors intended for use with a wide range of marketed drugs/biological products, the submission should include sterilization information for the injector, as recommended in the FDA guidance, *Submission and Review of Sterility Information in Premarket Notification (510(k)) Submissions for*

Devices Labeled as Sterile (Draft).[27] If the injector is provided as sterile, the data should demonstrate a probability of a non-sterile unit not greater than 1 x 10^{-6}. The components comprising the fluid pathway should be shown to be non-pyrogenic. For all sterile components, the submission should contain a description of the injector packaging, including a list of packaging materials. In addition, the sterility assurance necessary for the injector-drug/biological product in its final finished form the testing should be as recommended in the FDA guidance entitled, "*Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products."*[28]

FDA recognizes that the following standards may be useful for determining sterilization processes and test methods. The database of CDRH recognized standards is available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm

- ANSI/AAMI/ISO 17665-1: 2006, *Sterilization of Health Care Products – Moist Heat – Part 1: Requirements for the development, validation, and routine control of a sterilization process for medical devices*
- ANSI/AAMI/ISO 11135-1:2007,*Sterilization of Health Care Products – Ethylene oxide – Part 1: Requirements for development, validation, and routine control of a sterilization process for medical device*
- USP 27:2004, *Sterility, Biocompatibility, Biological Tests and Assays, Bacterial Endotoxin Test (LAL), Pyrogen Test (USP Rabbit Test), or other applicable tests related to the drug/biological product and delivery of the drug/biological product*
- AAMI/ANSI/ISO 11737-1:2006, *Sterilization of medical devices-microbiological methods-Part 1: Determination of the population of microorganisms on product*
- ANSI/AAMI/ISO 11607:2006, *Packaging for terminally sterilized medical devices*

For an injector that will be in a co-package or will be pre-filled with a specific drug/biological product, the submission should address the possible effects of the method of sterilization on the package (e.g., effects specific to the drug/biological product concerning, for example, light stability or oxygen sensitivity; effect on stability; effect on performance). For an injector cartridge that will be in direct contact with a drug/biological product, we recommend that you select an appropriate method of sterilization for the product and primary packaging material, and that you justify your choice of method in your submission. For example, if terminal

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[27] *Submission and Review of Sterility Information in Premarket Notification (510(k)) Submissions for Devices Labeled as Sterile (Draft*) available at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm109884.htm. When finalized this draft will supersede the FDA 2002 *Updated 510(k) Sterility Review Guidance K90-1*; http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM072790.pdf.

[28] *Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products,"* available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072171.pdf

sterilization will adversely affect the drug or biological product, you should justify the selected method for sterility assurance.

2. Cross-Contamination Potential

The vast majority of injectors are approved or cleared for single patient use. In general, multi-patient use injectors (e.g., reusable needle-free Multi-Use-Nozzle Jet Injectors) raise significant concerns for the risk of blood born pathogen and skin contaminant transmission from patient to patient. For example, there is a potential for disease transmission when blood contamination of the fluid path or the injectable product occurs during a previous injection. Contamination can occur on the skin-contacting surface of the injector or inside the injector from splash-back. It is also possible that the replaceable cap may become contaminated. In addition, in-between use cleaning of any component in or around the fluid path may result in contamination.

Sponsors are likely to face challenges in validating methods to evaluate the absence of cross-patient contamination. Initial information on such methodological challenges is available in the transcript of the FDA General Hospital and Personal Use Devices Advisory Panel meeting.[29] FDA strongly encourages sponsors who are considering the development of multi-patient use injectors to meet with FDA to discuss approaches to validate their testing methods and overall development plans. To facilitate discussion, FDA recommends that the sponsor submit a Pre-Submission, which should include, at a minimum, information on the use of the most sensitive test available, a discussion of test method selection, assumptions, limitations, plans to document the accuracy of this method, and a thorough discussion and justification of the test method selection.

H. Labeling

Pen, jet, and related injectors are intended for use by health care professionals, caregivers or for self-administration by the patient. We recommend developing labeling that carefully considers the end user and is consistent with the labeling of the drug or biological product for injection. (See section I.A.4 for the type of information that should be available in the approved labeling for the drug/biological product proposed for injection with the injector.) In some circumstances, it may be appropriate to develop a patient package insert or labeling for the patient or caregiver.[30] Additional instructions may be appropriate for in-service training programs to familiarize users with the features of the injector and how to use the injector in a safe and effective manner.

1. General Labeling Principles

[29] For more information, see the transcript for the FDA General Hospital and Personal Use Devices Panel (August 9, 2005), available at http://www.fda.gov/ohrms/dockets/ac/05/transcripts/2005-4172t1.htm.
[30] See 21 CFR 208.20.

In general, the following describes the appropriate elements that should be included in the labeling of the injector. As appropriate for how the injector and the corresponding drug/biological product are marketed (e.g., co-packaged, prefilled, or separately sold products), the labeling format should be tailored to ensure safe and effective use.[31]

- Injector description, including name
- Intended use and indications for use
- Type-of-use for the injector (e.g., personal, professional, single-use, reusable, labeled and sold for only one patient)
  a. Labeling should include appropriate warnings and precautions for the use conditions and patient population. For example, single-patient reusable injectors should include a warning to inform the user not to share the injector with other patients.
  b. Labeling on the injector itself should provide for space to allow healthcare provider to write the name of the specific patient for whom the injector is specified to avoid medication error.
  c. Labeling should include a prominent statement for "single patient use only" to avoid misuse and cross contamination.
- Intended patient population
- For general use injectors and those intended for use with a class/ family or a specific product line, sufficient labeling should be provided for the health care provider to determine what drug/biological product(s) is approved for administration by the injection method. As appropriate, this includes but is not limited to the following:[32]
  a. Language stating the readily identifiable characteristics of the class, family or product line of drug or biological products approved for use with the injector; e.g., characteristics that are in the drug/biological product labeling,
  b. Language referring the user to the approved drug/biological labeling to determine if it is specifically approved for use with that type of injector and to obtain relevant dosing information, or
  c. Language indicating that the injector is for use in accordance with the approved labeling of the drug/biological product.
  d. List of brand name or list of name, type, and characteristics of drug/biological product that is specifically approved for use with the type of injector, method of injection, the dose range for the

[31] The labeling format may vary depending upon the type of marketing application. For example, a general use device under 510(k) should provide sufficient information for a user to determine how to select an approved drug/biological product to inject using the injector. (Generally, see 21 CFR Part 801). For a combination product, the language will be specific for the device and drug/biological product. If the combination product is under NDA/BLA the format should be consistent with the Physician Labeling requirements available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm085169.htm.

[32] In developing final labeling, in addition to the data submitted, FDA considers the information on the approved drug label(s) provided in the submission, see Section I.A.4

injector, number of doses the injector delivers, single patient use or other conditions.

e. Drug/biological product capability (e.g., single-dose-disposable, repeat dose disposable, single patient reusable or refillable, adjustable dose).

- Contraindications
- Warnings, limitations, and precautions, including incomplete dosing, overdosing, dosing site error (e.g., injection into the incorrect tissue), and cross-contamination
- Safety and effectiveness data accrued with use of the injector
- Identification of any drug/biological product characteristics that are not compatible with the injector, if known
- Areas of the body appropriate for injection, including depictions with diagrams, and appropriate skin preparation prior to injection
- Target tissue and injection sites, including appropriate warnings for intravenous injection of drugs/biological products intended for intramuscular or subcutaneous injection
- Directions for use, user instructions, and diagrams. As appropriate, this should include instructions for use of the injector that is consistent with the approved drug labeling instructions
- Assembly instructions and diagrams (e.g., how the drug/biological product is contained in the injector and the method for inserting the drug/biological product into the injector)
- Maintaining sterility during injector assembly
- Dose setting and administering an injection
- How to ensure that the full dose is delivered
- How to ensure that a full dose remains in a reusable prefilled injector
- Prevention of or remedy for incomplete or partial dosing or overdosing events
- The correct amount of pressure needed for an injection
- Information about injection depth
- Labeling recommendations for sharps injury prevention features
- Environmental conditions of use and storage
- Reuse, cleaning, servicing
- Proper safe biomedical sharps waste disposal instructions for the injector, cartridge, and needles
- Troubleshooting
- Life of the injector and critical components

For injectors intended for use with a specified class/family or product line, FDA may request additional labeling information (e.g., expiration dating after insertion of the drug/biological cartridge into the injector and/or reconstitution of a drug cartridge, or use of nomenclature consistent with that of the drug/biological product).

Injector labeling should include a patient labeling and medication guide as applicable.

SECTION II: CONTENT AND FORMAT CONSIDERATIONS

FDA recommends a pre-submission meeting with the lead Center to discuss how you propose to organize the NDA/BLA Common Technical Document (CTD) submission to identify the injector related information. Similar meetings should be requested when an NDA/BLA submission is used along with a separate device submission. For additional information on stand alone 510(k) submissions, see 21 CFR Part 807 Subpart E. Also for process, content, and related information on all submissions see the links in Section III.

It should be noted that product codes are applicable to devices marketed under a device submission. When you include a pen, jet, or related injector in an NDA/BLA submission, you may reference the product code of a previously cleared injector and any associated information. As discussed in section I.B.1.(b), the reference to a 510(k) generally would not be sufficient, however, to address the safety and effectiveness of the device in the context of the use being proposed in the NDA/BLA submission (i.e., its use with a specific drug/biological product(s)).

SECTION III: WHERE CAN I FIND ADDITIONAL INFORMATION?

We recommend that you have early discussions with FDA if you are developing an injector described in this guidance and if you are uncertain about the type of technical and scientific information that may be appropriate or necessary in your submission. Such product-specific advice may be useful for complex delivery systems, for associated drugs/biological products, or for technical aspects of the device. Where appropriate, you may request a pre-submission meeting for more detailed discussion.

For injector systems associated with a new route, dose, rate or method of injection for the drug or biological product, FDA expects an inter-Center collaboration, as appropriate for the type of scientific and technical questions. If there are Center jurisdiction questions, we recommend that you contact the Office of Combination Products for additional information.

Additional guidance information is available from the CDRH, General Hospital Devices Branch at 301-796-2585 or from the Office of Combination Products by email to combination@fda.gov. General guidance information and links to the different center documents are also accessible at http://www.fda.gov/oc/combination/. For an injector intended for use with a specific drug/biological product, additional information is available from the CDER or CBER review division.

The following FDA guidance and informational documents may be useful when developing injectors intended for use with drugs and biological products.

- *Draft Guidance for Industry and FDA Staff – Applying Human Factors and Usability Engineering to Optimize Medical Device Design* (June 2011); http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm
- *Guidance for Industry and FDA Staff: Early Development Considerations for Innovative Combination Products* (Sept. 2006); http://www.fda.gov/RegulatoryInformation/Guidances/ucm126050.htm
- *Draft Guidance to Industry and FDA Staff: Current Good Manufacturing Practice for Combination Products* (Sept. 2004); http://www.fda.gov/RegulatoryInformation/Guidances/ucm126198.htm
- *Guidance for Industry and FDA Staff: Format for Traditional and Abbreviated 510(k)s* (August 2005); http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm084365.htm
- *The New 510(k) Paradigm - Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications - Final Guidance* (March 1998); http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080187.htm
- 21 CFR 807.87 -Information Required in a Premarket Notification Submission; http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=807
- *Guidance on Medical Device Patient Labeling;* http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070782.htm
- *Guidance for Industry, Formal Meetings with Sponsors and Applicants for PDUFA Products* (Feb. 2000); http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf
- *IND Meetings for Human Drugs and Biologics: Chemistry and Manufacturing Controls Information* (May 2001); http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070568.pdf
- *International Conference on Harmonization Q8(R2) Pharmaceutical Development* (May 2006); http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073507.pdf
- *Device Master File and Authorized Cross Reference Information:* http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/ucm142714.htm
- *Labeling for Human Prescription Drug and Biological Products – Implementing the New Content and Format Requirements;* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075082.pdf