

Draft Guidance for Industry and FDA Staff: Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products

DRAFT GUIDANCE

This guidance document is for comment purposes only.

Written comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

Additional copies are available from the Office of Combination Product, HFG-3; Office of the Commissioner; Food and Drug Administration; 15800 Crabbs Branch Way, Suite 200; Rockville, MD 20855; (Tel) 301-427-1934; (Fax) 301-427-1935; or <http://www.fda.gov/oc/combo>.

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**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.**

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Draft Guidance for Industry and FDA Staff

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

This draft guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic.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FDA is providing this draft guidance document to assist industry in developing technical and scientific information to support a marketing application for a pen, jet, or related injector device intended for use with drugs and biological products.¹ The marketing application would typically be a premarket notification submission (510(k)) or a premarket approval (PMA) application for the injector alone. For a combination product that includes the injector, the marketing application would typically be a New Drug Application (NDA) or a Biological Licensing Application (BLA).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.

This guidance does not apply to devices the sole purpose of which is to aid in the insertion of a syringe or infusion set. 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).

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.

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This draft 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.

The Least Burdensome Approach

This draft guidance document reflects our careful review of what we believe are the relevant technical and scientific development considerations for injectors and what we believe would be the least burdensome way of addressing these issues. If you have comments on whether there is a less burdensome approach, however, please submit your comments as indicated on the cover of this document.

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 may enhance safety, improve dosing accuracy, and increase patient compliance, particularly in self-administration settings. There are three basic groups of injectors. First, some injectors are intended for general use with a wide range of currently marketed drugs/biological products. Second, some injectors are intended for use with a certain class of drugs/biological products or with a specific product line. Third, some injectors are intended for use with a specific drug/biological product.

Depending upon the technology, an injector may be pre-filled with a drug/biological product for single or repeat dosing. For example, a given injector may be for single use only in acute intervention for treatment or prevention while another injector may be for repeat dosing as part of a long term treatment regimen. Other injectors may be available in a co-package with the drug or biological product for assembly by the patient or health care provider.

Pen, jet, and related injectors provide a method of accurately injecting a dose of drug/biological product³ from a cartridge, reservoir, or syringe through an automatically or manually inserted single lumen hypodermic needle or through a high velocity jet.

³ For purposes of this guidance, the phrase "dose of a drug/biological product" refers to a liquid, semi-solid, or solid form for injection by the device.

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They may be intended for use by a health professional or for self-administration by a patient, as appropriate, in the diagnosis, cure, mitigation, treatment, or prevention of disease.

Injectors may be subject to different regulatory provisions depending on their intended use, technological characteristics, proposed labeling, and packaging. For example, most injectors are intended for general use with a wide range of drugs/biological products and are marketed alone. Typically, general use injectors have marketing clearance as devices under a pre-market notification (510(k)). Other injectors are intended for use with a specific drug/biological product and may be pre-filled with that product, co-packaged with that product, or separately provided with mutually conforming labeling. These injectors are typically combination products under 21 CFR 3.2(e). For most combination products, one marketing application is sufficient for the injector and the drug/biological product; this application is usually an NDA/BLA. When appropriate, however, FDA may determine that two applications are necessary (i.e., an NDA/BLA along with a device submission that is usually a 510(k)). Considerations for determining the appropriate type of marketing application are beyond the scope of this draft guidance.

This draft guidance focuses on the scientific and technical considerations that may be relevant when developing a pen, jet, or related injector regardless of the regulatory provisions that apply (i.e., device, drug, or biological product provisions). It provides considerations applicable to a general use injector and to an injector intended for a product class, product line, or a specifically named drug/biological product. It also provides general content and format information for injectors to be reviewed under 510(k) submissions and for review as part of an NDA/BLA submission. It focuses specifically on scientific and technical information for the injector, which would be part of any marketing application. Overall, this draft guidance is intended to promote efficient premarket review and ensure consistent and appropriate postmarket regulation of injector delivery systems.

SECTION I: SCIENTIFIC AND TECHNICAL CONSIDERATIONS

A. Injector Description

Given the spectrum of use for injectors, we recommend that your submission comprehensively describe the product, its indication(s), and its conditions of use. Typically this information would include elements such as the following:

1. Identification

- Trade name or proprietary name of the injector
- Device regulatory classification and product code (see Section II for additional information if you are submitting a 510(k) submission)

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2. Indication Information

Proposed indication statement including the following items:

- Patient population (e.g., medical disorder, demographics)
- Injection site (area on the body where the drug/biological product is injected)
- Target tissue/required tissue characteristics
- Type-of-use (e.g., single, disposable, repeat dose, refillable)
- Identification of general use or indication of use with a product class, product line, or a specifically named drug or biological product

3. Description of Conditions of Use⁴

- Discussion of principles by which the injector operates
- Performance specifications
- Drug/biological product(s) of intended delivery
- Drug/biological product dose capability (e.g., single dose, multiple dose, adjustable dose)
- Description of how the injector is supplied to the end-user (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)
- Type-of-use and description of the intended user (if applicable), for example as arrayed in the following table:

Personal	For self-administration or by a non-professional caregiver
Professional	For use by a health care provider in a health care or institutional setting
Single-use	Entire injector and drug cartridge is discarded after a single use
Reusable	Injector can be used more than once with the same drug cartridge in place and is discarded after the cartridge is empty
	Injector can be used more than once with replaceable drug cartridge
Other	Describe any unique type-of-use characteristics

4. Description of Drug/Biological Product for Injection

As noted above, there are three groups of injectors: (a) injectors intended for use with a wide range of currently marketed drugs/biological products (general use), (b) injectors intended for use with a specific class or product-line of

⁴ Information in the "Conditions of Use" section may also be part of the "Labeling Indications" section or the "Use and Handling" section, as appropriate depending on the type of marketing application submitted (e.g., Structured Product Labeling in an NDA/BLA).

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drugs/biological products, and (c) injectors intended for use with only a specific drug/biological product. Overall, the descriptive information should reflect the following development considerations:

- a) **General use**: Typically, general use injectors would be marketed under a 510(k) premarket notification submission. A general use indication assumes the availability of at least one approved injectable product that is compatible with the injector.⁵ Further, it assumes that the injector will not change the characteristics of the marketed drug/biological product. For general use indications, the description section of your application should provide the following information on the drug/biological product to be used with your injector, in addition to the information recommended by other applicable guidance. As part of the review, FDA intends to consider how this information will be used in labeling to help ensure appropriate selection of a drug/biological product for the general use injector. (For additional information on labeling, see Section I.H.)
- Identify the drugs/biologic products that are currently approved and marketed for the dose, rate, and route of administration proposed for the general use injector. Your submission should include a copy or copies of the most recently approved labeling for representative drug/biological product(s) currently approved in a configuration (container-closure) that is compatible with your injector. (For additional information on performance testing for general use injectors, see Section I.D.)
 - Identify the drug/biological product characteristics, such as pH and viscosity, that are compatible with your injector materials and performance characteristics. You should also identify characteristics that would not be compatible with your injector materials and performance characteristics and/or provide a rationale for why certain characteristics were not tested.
 - If a compatible drug/biological product configuration is in development and/or pending approval, or if there are other compatibility concerns, we recommend that you contact the CDRH review branch or the Office of Combination Products for additional information.
- b) **Injectors intended for use with a class or product line or with a specific drug/biological product**: If the injector is intended to deliver a specific

⁵ In cases where only one marketed injectable product is available, FDA recommends that you discuss with the CDRH review branch or the Office of Combination Products whether to develop the injector as a general use device or as a device intended for use with that one approved product.

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drug/biological product, a certain product line, or a class of products, your submission should include the following.

- Identify the 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 of products is currently approved for the dose, rate, and route of injection proposed for the injector. We also recommend that you provide copies of the most recently approved product labeling of the target drug/biological product(s). For some very narrow or internally consistent product lines, it may be acceptable to provide a copy of the labeling for one representative product within the product line. (For additional information on performance testing for these products, see Section I.E.)
- Indicate whether the to-be-injected drug/biological product is already marketed in the necessary configuration in the injector.
- If you are proposing a new route, dose, or rate of administration for the drug or biological product, FDA expects that a CDER - CDRH collaboration will be necessary, as appropriate for the type of submission. We recommend that you contact the CDRH review branch or the Office of Combination Products for additional information.
- For pre-filled injectors and for injectors co-packaged with the drug/biological product, identify which application holder/manufacturer/supplier will perform the pre-filling, co-packaging, and other manufacturing steps.
- If you are providing injectors to pharmaceutical firms (or entities such as holders of other marketing applications) for further manufacture, pre-filling, or co-packaging, and if you wish to maintain certain confidential information, you can provide FDA with proprietary information about these injectors in a device master file. 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.⁶ These other entities could then reference the information in your device master file when they provide their own marketing submissions (i.e., NDA/BLA). In such circumstances, we recommend discussions with the Agency on what and how to provide information in the device master file and/or

⁶ For more information on master files (MAFs) and authorized references, see http://www.fda.gov/cdrh/dsma/pmaman/appdxc.html#P7_2.

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marketing application.

B. Design Features

Design features encompass the technical specifics of the injector, technical considerations for the injectable product, and the human factors to consider to ensure safety and effectiveness of the product.

1. Comparison to an Existing Delivery Method

To facilitate the regulatory review of the injector, developers may compare various design features to features in similar legally marketed products. The goal of this comparison may differ depending on the type of marketing application and development approach. For example, in a 510(k) submission, the comparison would be to a legally marketed predicate injector to demonstrate substantial equivalence.

When submitting a 510(k) submission, you should provide a comprehensive summary comparing and contrasting your injector with the predicate injector cleared under a different 510(k). In some instances, it may be appropriate to provide multiple comparisons. The following are examples of information and comparisons that FDA considers important in a 510(k) submission:

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

When submitting an NDA/BLA for approval of the injector, similar information

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may be useful.⁷ The NDA/BLA should also include either the specific information on the injector or a letter of authorization to reference information in a 510(k) or device master file that is necessary for review of the NDA/BLA.⁸ Note, however, that the referenced information may not be sufficient to address the safety or effectiveness (risk) of the device in the context of the use submitted in the NDA/BLA (i.e., use with a specific drug/biological product or products).

2. Engineering Drawings and Photographs

We recommend that you provide engineering component and assembly drawings for the injector and each of 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
- Drawings with critical dimensions and tolerances
- List of the components incorporated in the injector

3. Dose Setting and Administering an Injection

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

- Assembly of an 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
- Dose adjustment mechanism
- Resetting after use
- Needle change and disposal

We also recommend that you include:

- The source of power for the injector

⁷ Unlike in a 510(k) submission, the purpose of this information in an NDA/BLA would not be to establish substantial equivalence.

⁸ See footnote 6, above.

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- 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 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 for 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)
- If assembly by the user is required, details on how the injector is assembled; if the injector is pre-filled, details on 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 provided to aid proper dosing if:

- The injector is intended to deliver multiple doses of a drug/biological product
- The dose can be adjusted by the user
- The injector is intended to deliver a single dose of a specific drug/biological product and the risks associated with under- and 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.

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 such cases, the injector design should allow for appropriate inspection. For example, for a pre-filled injector, an injector that holds a cartridge for future use that cannot be removed once it is placed in the injector, or a repeat dose injector that uses the same drug cartridge after placement in the injector, the injector design should permit the full visual inspection of the injection material once it is placed in the injector pending later injection.

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In addition, some injectors are intended for use with high-risk drugs/biological products. When applicable, the injector design should address safety issues aimed at preventing confusion among different injectable products. Such design considerations may include, but are not limited to, special injector-cartridge design features that restrict use of a given cartridge to a specific injector, or injector-cartridge designs that allow a visual confirmation of the cartridge label to ensure the presence of the correct drug/biological product after placement in the injector.

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 the safety features of the injector, their purposes, and their procedures for use. Also, the submission should include details on all alarms, warnings, or switches and expected user responses to these features. 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/cdrh/ode/guidance/934.pdf>.

We also recommend that you conduct a risk analysis that considers the overall product and includes both the injector and injected material components. Specifically, you should assess the risk of use of the intended drugs/biological products delivered via a dedicated system. Furthermore, you should provide labeling information about conditions associated with the characteristics of the patient population using the intended drugs/biological products.

7. Human Factor Design Considerations

Depending on the characteristics of the intended use population or on the environmental conditions, the injector design may need to consider human factors that would affect the safety or effectiveness of the injector. These factors may include age, gender, range of tissue characteristics in the intended use population, medical disorders common to the end-user population, or environmental or other conditions associated with the intended use population.⁹ For example, injectors intended for use at high altitudes may necessitate special design features. Injectors intended for use in treating disorders associated with visual impairment or in treating arthritis may need design features that accommodate the visual impairment or manual

⁹ See *Guidance for Industry and FDA Premarket and Design Control Reviewers, Medical Device Use Safety: Incorporating Human Factors Engineering into Risk Management* (July 2000), available at <http://www.fda.gov/cdrh/humfac/1497.pdf>.

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dexterity, respectively, of the intended use population. Injectors intended for use by the military may need to accommodate special environmental conditions under which the products will be stored and possibly used (e.g., desert and tropical climates, frigid conditions, at various altitudes, in aircraft, and in submarines below sea level). (See also Section I.F for further discussion of human factors.)

C. Injector Materials of Construction and Manufacture

Your marketing application should identify all known materials that comprise the injector for use as well as the manufacturing materials used in construction of the injector. Specifically, for each material or component, the submission should provide the chemical, grade, and brand name and indicate which materials are in or will affect the fluid path.¹⁰ It should also identify any components that are not identical to those of the predicate injector or other delivery mode, for example, plastic stoppers instead of glass stoppers. (See Section I.B.1 for more on such comparisons.) For any new component, the submission should include the methods and results of biocompatibility tests.

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). Furthermore, some products such as lyophilized drugs may be more sensitive to moisture, and other products (e.g., solutions) may be more sensitive to oxygen. The submission should therefore include the results of tests that examine the interaction of the drug/biological product with the injector. These tests should explore how the injector-drug/biological product interactions affect each other's performance. They should include the entire product use cycle, ranging from materials that interact with the drug/biological product within the cartridge or injector to the injection process itself.

The following list describes specific issues FDA intends to consider in reviewing the submission:

- Analysis of potential 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)
- Effect of adsorption of drugs/biological products (including preservatives) on injector components
- Effect of head-space volatile compounds and impurities on the drug/biological product and/or injector components
- Effect of drug-injector interaction over time for re-useable injectors
- Analysis of functional materials corrosion from the drug/biological product

¹⁰ For purposes of this guidance, materials that are in or will affect the fluid path are components and accessories of the injector that contact the drug/biological product, including the needle, dose chamber, cartridge, plungers and stoppers, and reservoirs for the drug/biological product.

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- Analysis of seal integrity (e.g., lubricity breach of sealing)
- Introduction of particulates

D. Performance Testing: General Use Injector Considerations

Performance testing for general use injectors should consider the characteristics of drugs/biological products and diluents with which your injector is intended to be used. For example, these tests should study a range of drugs/biological products for appropriate reconstitution with a range of diluents (e.g., aqueous, non-aqueous, or oil based). For each injectable product and delivery vehicle used for 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. FDA recognizes that in some general use circumstances it may be acceptable to conduct testing with a range of alternative substances. If such testing is proposed, the submission should provide a detailed justification for why it is appropriate and why the chosen substance or range of substances is acceptable. When conducting performance testing, we recommend that you follow the standards identified below and available at

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm>:

- *ISO 7886-1:1993, Sterile Hypodermic Syringes for Single Use - Part 1: Syringes for Manual Use*
- *ISO 10993-1:1997, Biological Evaluation of Medical Devices - Part 1: Evaluation and Testing*
- *ISO 11608:2000, Pen-Injectors for Medical Use*
- *ISO 21649:2006, Needle-Free Injectors for Medical Use - Requirements and Test Methods.*
- *ASTM D4169:1999, Standard Practice for Performance Testing of Shipping Containers and Systems*
- *ASTM F647, Testing to Assess Durability of Devices Following Interaction with Drugs*

FDA also recommends that you conduct software and electromagnetic compatibility testing as appropriate for your injector. Guidance on these aspects is available from FDA.¹¹

FDA recommends that your submission include results from the performance tests identified below. Your submission should include not only the results of each test, but also a diagram of each test set-up (with labels to identify the test instruments) and an explanation of how each test was conducted.

1. Biocompatibility

¹¹ See *General Principles of Software Validation; Final Guidance for Industry and FDA Staff* (Jan. 2002), available at <http://www.fda.gov/cdrh/comp/guidance/938.pdf>; see also <http://www.fda.gov/cdrh/emc/>.

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For general use injectors, FDA recommends that you conduct biocompatibility testing as described in the guidance, *Use of International Standard ISO-10993, Biological Evaluation of Medical Devices Part-1: Evaluation and Testing* (May 1995), available at <http://www.fda.gov/cdrh/g951.html>. The 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 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:

- 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> and USP<88>¹² 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.

2. Shelf-Life Stability and Expiration Dating

For stability and expiration dating, the testing should consider the injector alone and the injector with the drug/biological product. For the injector alone, the data should demonstrate that the injector can be reliably and reproducibly used for the labeled number of injections. FDA recommends that shelf life-testing endpoints include:

- Freedom from defects (e.g., displaced parts, cracking, leaking)
- Dose accuracy (see Section I.E.1)
- Replacement needles and cartridges

The submission should include an analysis and discussion of the physical degradation and changes to the injector due to the conditions the injector is exposed to before use (i.e., shelf life, expiration date) and during use (in-use life expiration dating). For additional information relating to the life of an injector, see Section I.E.1.

¹² United States Pharmacopeia information is accessible at <http://www.usp.org>.

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When determining the stability and shelf life, expiration date, and in-use life expiration date, 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
- Extreme storage temperature environments
- Extreme conditions of use testing, when applicable
- Packaging
- Shipping

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.

3. Functional Testing

Depending on the injector design, it may be appropriate to conduct additional bench testing to demonstrate the functionality of the injector. Testing to assess the reliability 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 (see Section I.E.2)
- Functionality of the safety mechanism
- 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 injector and injector labeling are not adversely affected by the recommended cleaning agents)
- Structural testing at extreme pressure and temperature conditions

Testing to assess the mechanical features 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

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- 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 safety features to ensure their intended performance. Also, for multiple use injectors, the testing should establish the duration of repeated use.

For a general use injector, we further recommend performance testing for dose accuracy and route of injection (see Section I.E.1-2).

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

In developing your plan for performance testing of injectors intended for use with a certain class/product line or with a specific drug/biological product, you should begin with the considerations described in Section I.D and should then focus on the unique injectable product. Depending upon the specific materials in the product, FDA may request additional pharmacology-toxicology testing.

When conducting performance testing for your injectable product, you should use the actual drug/biological product(s) 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 of products, 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 absence of leachable material into the drug/biological product. This testing should include testing for extractables (more below). In addition, you should identify which drug/biological product characteristics were tested and the methods used to demonstrate absence of adherence to the injector materials.

Specifically, 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

FDA recommends completion of the following dose accuracy testing.

- 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 cartridge injectors satisfy the requirement

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- that each successive dose is the same as the first set dose
- Testing to ensure that dose settings/markings correlate with the volume of drug/biological product delivered

Because diluents may affect the drug/biological product and the injector, the above testing should ensure that the delivery volume meets the dose accuracy specification for the specific drug/biological product when reconstituted according to its approved or proposed labeling, as applicable.

We recommend, where appropriate, that injectors include a mechanism or feature that notifies the user that an incorrect dose has been delivered. Performance testing should include testing of such mechanism(s). Product labeling should also include information instructing the user on what action should be taken in the event of incorrect dosage.

2. Depth and Route of Injection

Testing should demonstrate that the depth of needle penetration and/or dispersion of the injectate are consistent. The model chosen for testing should simulate human skin and any specific tissue layers as closely as possible. The application should include an explanation to justify the model chosen for testing.¹³

Where applicable, the submission should include the results of studies to compare the depth of penetration and dispersion testing of the subject injector with similar injectors or other methods of delivery. It should also include a statistical comparison and a discussion of, and justification for, any differences between the measurements for the subject injector and those for similar injectors or other methods of delivery.

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, amount delivered epidermally, amount delivered intramuscularly).

For injectors that involve the mechanical actuation and insertion of the hypodermic needle, we recommend that you perform additional testing. Testing should examine the following parameters:

- Reliability for the specified depth of insertion throughout the expected injector life cycle

¹³ Submissions for previously cleared or approved injectors have included depth of penetration testing performed on human, porcine, and cadaver models.

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- 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 (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 drug/biological product. In some circumstances, similar testing may be appropriate for injectors intended for use with a class/product line.

- **Extractability/Leachability**

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 types of injection media 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: pH shift, turbidity, heavy metals, non-volatile residue, residue on ignition, UV absorption, silicone content, etc.
- Chromatography: nucleating agents, cross-linking agents, curing agents, antioxidants, acid scavengers, plasticizers, etc.
- Impurities and degradation products
- Endotoxins

- **Adsorptivity**

Testing should ensure that there is no tendency for gases, liquids, or solutes to accumulate on a surface of the drug/biological product.

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

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When the injector 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/cber/gdlms/cntanr.htm>.

- **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 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 and that may degrade and contribute to the denaturing of the drug/biological product.

Further, 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 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 the injector alone, see Section I.D.2.)

F. Performance Testing: Clinical Considerations

Specific considerations for clinical trial design are beyond the scope of this guidance. In general, however, clinical trials for some injectors may focus on the injector itself. Typically, these trials would evaluate the design features and whether the intended use population can use the injector as proposed.

1. Human Factors

In some instances, depending upon the characteristics of the injector, studies may be appropriate to demonstrate that providers or patients can use the injector properly. Sometimes these studies may focus on general use performance, for example the ability of users to read and follow instructions for set-up and use. In other instances, the studies may focus on specific factors, characteristics, and demographics of the intended use population. These factors may include age, gender, range of tissue

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characteristics in the intended use population, disorders commonly seen in the intended use population, or environmental or concomitant conditions associated with the intended use population.¹⁴ For example, for an injector intended for use with a drug for treatment of arthritis, studies should test whether the design accommodates the manual dexterity of the target patient population.

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 injectors or complex dose-adjustment methods. For such products, we recommend that you contact the lead review division to discuss the pre-clinical and clinical development plan.

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 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 in accordance with the FDA guidance, *Updated 510(k) Sterility Review Guidance K90-1; Final Guidance for Industry and FDA* (August 2002), available at <http://www.fda.gov/cdrh/ode/guidance/361.html>. If the injector is provided as sterile, the data should demonstrate a probability of a non-sterile unit not greater than 1×10^{-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.

FDA recognizes that the following standards may be useful for determining sterilization requirements and test methods. These standards are available at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm>.

- *ANSI/AAMI/ISO 11134:1993, Sterilization of Health Care Products – Requirements for Validation and Routine Control – Industrial Moist Heat Sterilization*
- *ANSI/AAMI/ISO 11135:1994, Medical Devices - Validation and Routine Control of Ethylene Oxide Sterilization*
- *USP 27:2004, Sterility, Biocompatibility, Biological Tests and Assays, Bacterial*

¹⁴ See *Guidance for Industry and FDA Premarket and Design Control Reviewers, Medical Device Use Safety: Incorporating Human Factors Engineering into Risk Management* (July 2000), available at <http://www.fda.gov/cdrh/humfac/1497.pdf>.

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- 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 11737-1:1995, Sterilization of medical devices-microbiological methods-Part 1: Estimation of the population of microorganisms on product
 - ANSI/AAMI/ISO 11607:2000, 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 co-package sterilization on the combination product (i.e., effects specific to the drug/biological product concerning, for example, light stability or oxygen sensitivity). 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 you do not use aseptic methods, you should justify this choice.

2. Cross-Contamination Testing

Disease transmission may result from cross-contamination in reusable needle-free injectors, e.g., Multi-Use-Nozzle Jet Injectors (MUNJIs). There is a potential for disease transmission when blood contamination of the fluid path or 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.

Given these risks of contamination, submissions for MUNJI injectors should provide cross-contamination testing results and should quantify the residual contaminant for subsequent injections. The submission should identify the test method chosen for quantifying the residual contaminant, indicate the accuracy of this method, and include a thorough discussion and justification of the test method selection. In general, the most sensitive test method available should be used. The discussion of test method selection should include assumptions, limitations, and weaknesses of the test method. Also, the bench testing for blood cross-contamination should include testing for hepatitis B virus (HBV), using the most sensitive detection method available.¹⁵

In addition, FDA generally recommends against developing injectors that require between-use cleaning of any component in or around the fluid path. If such cleaning is necessary, the review division should be contacted for additional guidance.

¹⁵ For more information on cross-contamination risks and detection of HBV, 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>.

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H. Labeling

Pen, jet, and related injectors may be intended for use by health care professionals or for self-administration by the patient. Overall, the submission should include clear and concise instructions that delineate the technological features of the specific injector and how the injector is to be used. We recommend developing labeling that carefully considers the user. In some circumstances, it may be appropriate to provide a patient package insert or labeling for the patient or caregiver.¹⁶ 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. The following examples illustrate the elements that may be appropriate for labeling.¹⁷

- Injector description, including name
- Intended use and indications for use
- Type-of-use for the injector (e.g., personal, professional, public health, single-use, reusable, DCJI, MUNJI, labeled and sold for only one patient)
- Intended patient population
- Name, type, and characteristics of drug/biological product that is compatible with the injector, the dose range for the injector, and number of doses the injector delivers
- Drug/biological product approval status (FDA or USP)
- Drug/biological product capability (e.g., single-dose-disposable, repeat dose disposable, repeat dose refillable, adjustable dose)
- Directions for use, user instructions, and diagrams
- Areas of the body appropriate for injection, including 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
- Warnings, limitations, and precautions, including incomplete dosing, overdosing, misdosing (injection into wrong tissue), and cross-contamination
- Contraindications
- Identification of any drug/biological product(s) that are not compatible with the injector
- 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

¹⁶ See, e.g., 21 CFR 208.20.

¹⁷ The labeling format may vary depending upon the type of marketing application submitted.

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- 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 including validation methods
- Labeling recommendations for sharps injury prevention features
- Environmental conditions of use and storage
- Reuse, cleaning, servicing, and disposal instructions
- Troubleshooting
- Life of the injector and critical components

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

SECTION II: CONTENT AND FORMAT CONSIDERATIONS

A. Preliminary Format Considerations for an Injector in an NDA or BLA Submission

Some applicants who have included injector information in an NDA/BLA have included the injector information under the Common Technical Document (CTD) as a subsection in module 3. Other applicants have included the information in the container closure section. FDA recommends a pre-submission meeting with the lead center to discuss how you propose to organize the NDA/BLA submission. Similar meetings should be requested when an NDA/BLA submission is planned along with a 510(k).

It should be noted that product codes are applicable to devices marketed under device regulatory provisions only. When you include a pen, jet, or related injector in an NDA/BLA submission, you may reference the product code of a previously cleared or approved injector and any associated information. This referenced information may not be sufficient, however, to address the safety and effectiveness (risk) 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)).

B. Abbreviated 510(k) Submission Considerations

When a 510(k) is appropriate for a pen, jet, or related injector, you have the option of submitting a Traditional 510(k), an Abbreviated 510(k), or a Special 510(k).¹⁸ For the general use injectors discussed in this document, FDA believes that an Abbreviated

¹⁸ FDA has published several guidances on 510(k) submission methods, available at <http://www.fda.gov/cdrh/ode/parad510.html> and http://www.fda.gov/cdrh/ode/92_a.html.

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510(k) is generally acceptable and provides the least burdensome means of demonstrating substantial equivalence.

Pen injectors are generally regulated as class II devices under 21 CFR 880.5860 (product code NSC) and 21 CFR 880.6920 (product code KZH).¹⁹ Jet injectors, which include needle-free or needless injectors, are generally regulated as class II devices under 21 C.F.R. 880.5430 (product code KZE).

For 510(k) format and content information, you should refer to the following:

- 21 CFR 807.87
- *The New 510(k) Paradigm - Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications; Final Guidance* (March 1998), available at <http://www.fda.gov/cdrh/ode/parad510.html>
- *Guidance for Industry and FDA Staff: Format for Traditional and Abbreviated 510(k)s* (August 2005), available at <http://www.fda.gov/cdrh/ode/guidance/1567.pdf>

If you are a manufacturer considering modifying your own cleared device, it may be possible to lessen the regulatory burden by submitting a Special 510(k). If so, then FDA recommends that you include the technical information, as applicable, in the Special 510(k) submission using the format recommended in the preceding guidance documents. The Special 510(k) should describe the risk analysis method used and the results of this analysis. If you elect to use an alternative approach to address a particular risk identified in this draft guidance, or if you have identified and addressed risks additional to those identified in this draft guidance, your Special 510(k) should provide sufficient detail to support review of the risk analysis method chosen.

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 draft 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.

Additional guidance information is available from the CDRH, General Hospital Devices Branch at 301-240-276-3707 or from the Office of Combination Products by email to combination@fda.gov. General guidance information and links to the different center

¹⁹ In identifying injectors, FDA distinguishes pen injectors from piston syringes and pen injectors with manually-inserted needles from pen injectors with automatically-inserted needles.

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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.

- *Guidance for Industry and FDA Premarket and Design Control Reviewers, Medical Device Use Safety: Incorporating Human Factors Engineering into Risk Management* (July 2000), available at <http://www.fda.gov/cdrh/humfac/1497.pdf>
- *Guidance for Industry and FDA Staff: Early Development Considerations for Innovative Combination Products* (Sept. 2006), available at <http://www.fda.gov/oc/combination/innovative.pdf>
- *Draft Guidance to Industry and FDA Staff: Current Good Manufacturing Practice for Combination Products* (Sept. 2004), available at <http://www.fda.gov/oc/combination/OCLove1dft.pdf>
- *Guidance for Industry and FDA Staff: Format for Traditional and Abbreviated 510(k)s* (August 2005), available at <http://www.fda.gov/cdrh/ode/guidance/1567.pdf>
- *The New 510(k) Paradigm - Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications - Final Guidance* (March 1998), available at <http://www.fda.gov/cdrh/ode/parad510.html>
- *Guidance for Industry, Formal Meetings with Sponsors and Applicants for PDUFA Products* (Feb. 2000), available at <http://www.fda.gov/cder/guidance/2125fnl.pdf>
- *IND Meetings for Human Drugs and Biologics: Chemistry and Manufacturing Controls Information* (May 2001), available at <http://www.fda.gov/cder/guidance/3683fnl.pdf>
- *Early Collaboration Meetings under FDAMA; Final Guidance for Industry and CDRH Staff* (Feb. 2001), available at <http://www.fda.gov/cdrh/ode/guidance/310.pdf>
- *International Conference on Harmonization Q8 Pharmaceutical Development* (May 2006), available at <http://www.fda.gov/cder/guidance/6746fnl.pdf>