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July 27, 2009

Dockets Management Branch (HFA-305)
Food and Drug Administration
5600 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2009-D-0179, Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the *Draft Guidance for Industry and FDA Staff: Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products*.

BIO represents more than 1,200 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnology products, thereby expanding the boundaries of science to benefit humanity by providing better healthcare, enhanced agriculture, and a cleaner and safer environment.

BIO agrees with FDA's assessment that "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." (Lines 56-58) Indeed, the innovation of the biotechnology industry extends into drug delivery, and novel injector approaches are improving the convenience of administering drugs, minimizing pain and suffering, and maximizing medical outcomes for patients. Injector technologies are rapidly evolving as pre-filled pens, jet, and needleless technologies become more common. However, these advancements also pose the question of what regulatory submissions should be provided to FDA to assure the

safety and reliability of new injector systems. BIO applauds FDA for releasing this draft guidance to industry and seeking to establish the least burdensome approach for regulatory submissions regarding pen, jet, and related injectors. We are pleased to offer the following general and technical comments in support of the guidance.

GENERAL COMMENTS:

Our comments primarily fall under three general areas which address concerns that the guidance as currently drafted: (1) does not represent a least burdensome approach; (2) does not address application of Risk Management and or Quality System requirements in determining the need for scientific and technical information to support device submissions; and (3) does not address how the issuance of this guidance will impact current products in the market. Under our general comments we list specific comments that support our general concerns where appropriate.

I. Not Representative of the Least Burdensome Approach:

This guidance does not achieve the least burdensome approach in addressing technical and scientific development considerations for injectors particularly in the areas of: (1) data requirements, (2) product classification, and (3) labeling requirements.

1. **Data Requirements:** The guidance addresses a broad spectrum of devices (*e.g.*, devices that are mechanical vs. devices that are electromechanical, devices that are general use vs. devices/combination products that are specific use) and provides recommendations for the scientific and technical data needed to support marketing applications covering all of them without distinction between the complexity of the different devices or their intended use. As a result the guidance fails to provide a least burdensome approach in particular for general use injectors and New Drug Applications (NDA) or Biologic License Applications (BLA) in which an injector is already approved.

   Rather than providing a list of requirements covering all devices, regardless of complexity or intended use, the guidance should address the requirements for specific classes of devices having comparable features. We recommend that the agency consider including a table or a series of tables that specify data expectations for common injector categories (*A proposed table format can be found in the appendix to these comments).* Under this approach, the table could list the specific submission and testing expectations for a base case for a typical injector configuration and then provide additional considerations for the more complex scenarios.

   Specific examples in the guidance of overly burdensome data requirements can be found in the specific comments section addressing: line 165-185; line 181-185; line 239; line 282-294; line 298-366; line 476-479; line 628-629; line 632-636; line 634-636.

2. **Existing FDA Guidance on Submission Requirements and Product Classification Codes for Piston Syringes and Pens:** Submission requirements for piston syringes and pen injectors are covered in an existing FDA guidance document, *Guidance on the Content of*

Premarket Notification Submissions for Piston Syringes. Pen injectors fall under very broad product classification codes so applicability of guidance for these devices in the existing FDA guidance and the proposed draft guidance could force manufacturers to comply with two separate and at times conflicting guidance documents. This certainly would not qualify as a least burdensome approach. We recommend that FDA clarify expectations regarding applicability of guidance to specific classes of devices covered by the different guidance documents or state whether the new guidance document will replace the existing guidance document which covers piston syringes and pens.

3. **Labeling Requirements:** The draft Injector guidance provides overly burdensome requirements for labeling. Instead of including specific requirements for labeling in the guidance, it would be more appropriate to reference the labeling requirements of 21 CFR Part 801 and existing Center for Devices and Radiological Health (CDRH) guidances for patient labeling.

   Specific examples in the guidance of overly burdensome labeling requirements can be found in the specific comments section addressing: line 296-333; Section I.H Labeling: line 830-865.

II. Application of Risk Management and or Quality System Requirements in Determining the Need for Scientific and Technical Information to Support Device Submissions:

BIO requests that the guidance discuss the application of Quality Systems, use of risk assessments in device development, or specific requirements associated with self-administration/home use of a product.

The application of quality systems is a key issue that is not addressed within the guidance document. The confusion around the application of quality systems is a well known issue with combination products. We recommend that the agency provide direction on how to balance the differences between Part 820 and Parts 211/600, especially for topics like Design Controls and Purchasing Controls, as these topics are very relevant to the development of the type of products covered by this guidance and help guide technical requirements and documentation. For example, the guidance document refers to design verification and validation activities that would generally take place as part of design controls for a medical device, but does not mention the necessity for documenting the design inputs that define what is tested through design verification and validation. In addition the guidance does not address planning for this testing as would be done in a Design and Development Plan, nor does it address where this data should be kept, for example in a Design History File. Another critical area to address in the guidance document would be Purchasing Controls. With combination products there is often a device company working with a pharmaceutical company, and there is a need to clarify expectations for setting specifications for purchased materials and provide direction on acceptance procedures and sampling for incoming inspection.

Another area that is inadequately addressed is the application of risk management in device development. This should be clearly identified as a decision making tool for manufacturers, to determine the requirements they will need to meet based on the level of risk associated with use of a device in patients. The guidance would be less burdensome if the recommend requirements were

triaged by risk. Further, it would be helpful if the guidance document provided some insight on how to balance the application of the device Risk Management standard (ISO 14971:2007) and the drug Risk Management standard (ICH Q9). As currently drafted it appears as if every device, regardless of risk or complexity, would be expected to follow each recommendation in the guidance.

Specific examples in the guidance of how application of risk assessment could be used in making decisions regarding the data recommendations for specific injection devices can be found in the specific comments section addressing: line 408-415; line 439; line 584-585; line 625; line 653-655; line 713-720.

III. Legacy Products and Post Approval Changes:

This guidance addresses the technical and scientific information needed to support a marketing application for a pen, jet, or related injector device intended for use with drugs and biological products, but does not address the reporting requirements and data needed to support post approval changes to an already approved injector device used with a drug or biological product. Post approval changes to an injector submitted for approval in the drug or biological product license would typically be reported in a supplement to the NDA or BLA. However, guidance as to the applicability of suggested reporting requirements under drug/biologic or device regulations for changes to the injector is not provided. We recommend that FDA clarify that legacy products and future supplements for those products are outside of the scope of this guidance. In addition, clarity is needed on the applicability of the recommendations in this guidance to already approved injector/pen products or relevant combination products already in the market place.

CONCLUSION:

BIO appreciates this opportunity to comment on *Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products.* We have provided specific comments in Appendix 1 and a proposed table format for describing data requirements for specific injector classes in Appendix 2. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

Andrew J. Emmett
Director for Science and Regulatory Affairs
Biotechnology Industry Organization (BIO)

APPENDIX 1: SPECIFIC COMMENTS

Line #	Criticality	Change Requested and Justification	Recommended Change
N/A	Medium	We request clarification regarding the extent of data presentation in the application itself for combination products and which data are to be considered inspectable.	Please clarify that summary data are to be presented in the submission and the full data packages are reviewable upon inspection.
INTRODUCTION, LEAST BURDENSOME APPROACH, AND BACKGROUND			
21		It is not clear if the reference to 510(k)s or Premarket Approval Applications (PMA) being filed for an "injector alone" is meant to apply to injectors that are packaged separately and therefore "alone" or if their indication for use is as a general use injector.	Please replace the term "injector alone" with "general use injector".
21		Since the type of filing associated with a combination product is determined by the primary mode of action of the product, it would help the reader to clarify that typically NDA or BLA are the marketing application that is used when the primary mode of action is the drug or biologic.	Please edit the sentence to read (additions in <u>underlined font</u>): For a combination product that includes an injector the marketing application would typically be a NDA or a BLA, <u>if the primary mode of action is the drug or biologic.</u>
21-23	High	It is not clear from the draft guidance if reference to NDA or BLA includes the use of prior-approval supplements.	Please clarify that a prior-approval supplement to an NDA/BLA may be used for introduction of a new injector combination product for an already approved drug/biological product.
58-62		It is unclear what the distinction would be between injectors with a certain class of drugs/biologics or a specific product line and	We recommend that the groups be those intended for general use and those used as combination products.

Line #	Criticality	Change Requested and Justification	Recommended Change
		those for use with a specific drug/biological product.	
87-89		It is unclear under which circumstances FDA may determine that two applications are necessary (*i.e.*, an NDA/BLA (BLA) along with a device submission that is usually a 510(k)).	Please clarify the scenario in which two marketing applications would be required for the same product rather than cross-center collaboration between the Center for Drug Evaluation & Research (CDER) or the Center for Biologics Evaluation & Research (CBER) and Center for Devices & Radiological Health (CDRH).
89	Medium	The guidance explains that considerations to determine the appropriate type of marketing application are beyond the scope of the document.	Please consider adding references to available guidances (*e.g.*, combination products guidance, device classification, etc.).
SECTION 1: SCIENTIFIC AND TECHNICAL CONSIDERATIONS			
A. Injector Description			
114		The draft specifically recommends inclusion of the trade name or proprietary name of the injector.	We recommend that the generic/established name should be included together with the trade/proprietary name to comprise the full name of the device in the submission.
123		Please clarify what is meant by target tissue characteristics; does it refer to injections delivered subcutaneously, intradermally, or intramuscularly?	Please clarify.
165-185		The requirements in this section for the description of the product for general use devices appear to reflect the worst case scenario for most complex devices and seem excessive for simple devices such as piston driven	Rather than identifying specific products and their characteristics it might be more appropriate to list the scope of products and their physical, biological or chemical properties that would or would not be

Line #	Criticality	Change Requested and Justification	Recommended Change
		syringes. In addition, it is difficult to imagine how the manufacturer of a general use device would be able to anticipate the full spectrum of products that might be used.	appropriate for use with the device.
181-185		It is unclear how a device manufacturer would be able to address the requirements in this bullet. For example, how would the device company know of development plans or submissions in review unless they were partnered with a specific drug company and therefore, not a general use device. Additionally, it is not clear what questions the company could ask the FDA regarding products under development that might be used with their device.	We recommend deleting this bullet.
187-231	High	The rationale for distinction between injectors with a certain class of drugs/biologics or a specific product line and those for use with a specific drug/biological product is unclear as the data requirements appear to be the same. As suggested, permitting use of representative data instead of repeat testing with all drugs intended to be used as a combination product with a specific injector will allow a least burdensome approach.	Please consider allowing use of "representative" and/or "bracketing" data if the injector is intended to be used with multiple products.
B. Design Features			
239		The section on Design Features does not distinguish between general use devices and devices used with a drug or biologic product.	The section on Design Features should distinguish between requirements for general use devices, devices used with drug or biologic products, or state how such information could be cross referenced in a PMA,

Line #	Criticality	Change Requested and Justification	Recommended Change
			510(k) or device master file.
253-271		The examples of information and comparisons that FDA considers important in a 510(k) submission implies that all the information listed in this section must be included as required design features for all devices. The guidance should allow for a risk based approach to applying requirements to specific devices rather than implying all of this information is needed for all devices.	We suggest modifying the sentence preceding examples in lines 253-271 to read: "The following are examples of information and comparisons that FDA may consider to be applicable for a 510(k) submission based on the complexity of the device:"
274-280		Presumably information in lines 253-272 comparing the injector to an existing delivery method would be covered in cross reference(s) to information in a 510K or device master file for a combination product.	Please add a statement that this information would only be needed if the device was not already approved or cleared.
278-280	Medium	It is unclear what specific information the agency requires to assess the safety and effectiveness of the injector. Does this refer to information on the specific drug/biologic used in a combination product?	Please either explain what additional information might be necessary to establish the safety or effectiveness (risk) of the injector or provide a reference where the information might be found.
282-294		The guidance implies that engineering drawings and photographs are necessary for all submissions. However, in some instances, an applicant may not be able to provide such drawings and photographs, unless the applicant developed the injector device.	Add a statement that this information can be cross referenced in a 510K or DMF for a combination product.
296-333		Information needed for setting and administering the dose is included in the Instructions for Use (IFU) (Section H.	We recommend deleting these requirements from this section.

Line #	Criticality	Change Requested and Justification	Recommended Change
		Labeling). Providing this information here is redundant.	
298-366		The wide variety of requirements presented makes it difficult to determine what should apply to a specific injector type. Further, lines 299-301 make reference to comparing reliability and reproducibility to a predicate injector, without clarifying that such issues are appropriate for a 510(k) submission, rather than an NDA/BLA. Clarifications such as these are critical to ensure industry and FDA staff are clear on what information a submission should include.	Rather than providing a list of recommendations covering all devices, regardless of complexity or intended use, the document should provide guidance on requirements for specific classes of devices having comparable features.
342	High	There are several other reliable means of ensuring accurate delivery of a single, fixed dose. Pharmaceutical and biotech companies have successfully applied process and primary container design, validation, in-process controls and lot release testing to ensure precision and reproducibility in deliverable volume of liquid formulations. There are several scenarios where graduation marks/fill may be impractical or unreliable, *e.g.*, if the primary container is made by blow molding glass that is prone to variability in internal dimensions.	We suggest removing the recommendation for graduation marks/fill lines for injectors intended to deliver a single, fixed dose.
346 - 347		The guidance provides that graduation marks and fill lines may be used to aid in setting and verifying dosage. However, graduation marks and fill lines can also be used to ensure that during transport of finished product that there	Please edit this sentence to read (additions in <u>underlined font</u>): "When using graduation marks or fill lines <u>to aid the user in setting the correct dose or for verifying the set dose,</u> the submission should include validation."

Line #	Criticality	Change Requested and Justification	Recommended Change
		are no gross leaks in the container closure system. In such a case, fill lines may be placed after the filling process and validating the accuracy of the marking it is not necessary.	We suggest that the full data package that support the accuracy of graduation marks or fill lines should be subject to review upon inspection rather than having the full data package provided in the submission.
357	Low	The draft guidance points out that "in some circumstances" the product for delivery is labeled to require visual inspection of the product before injection. On lines 352-3, it states that, *"In such cases, the injector design should allow for **appropriate** inspection."* (emphsis added) Lines 354-58 provide useful examples, but the sentence concludes with the statement that in such cases *"...the injector design should permit the **full** visual inspection of the injection material once it is placed in the injector pending later injection."* (emphasis added).	"Appropriate" inspection more accurately describes the standard that should be applied. Use of two different descriptors for the same attribute within the guidance has the potential to create confusion and uneven implementation of the guidance when finalized. Accordingly, we recommend replacement of the word "full" with the word "appropriate" in line 356 for both consistency and accuracy in conveying the necessary attributes of the injector
360		The rationale for this change is to eliminate confusion in the definition of "high risk" items. This will help ensure consistency in approach both within industry and among FDA reviewers. However, we do note that it can be difficult to put a precise definition on high risk items. They could be cytotoxic drugs, antibody drug conjugates, radiolabeled drugs, different dosage strengths, etc. We assume that the point to this section is that injectors need to be designed to assure they are used with the correct drug or biologic product whether high risk or not.	Please define what is meant by "high-risk" drugs/biological products and clarify that injectors need to be designed to assure they are used with the correct drug or biologic product whether high risk or not.

Line #	Criticality	Change Requested and Justification	Recommended Change
397	Medium	Design features for injectors intended for use at high altitudes or other extreme conditions should be referenced in appropriate ASTM International and International Organization for Standardization (ISO) standards for usability.	Please provide reference to appropriate usability standards at the end of this sentence to guide the applicant in the types of design features needed for use at high altitude.
C. Injector Materials of Construction and Manufacture			
408 - 415	Low	The requirement for identifying all known materials comprising the injector and all manufacturing materials used in construction of the injector goes far beyond current expectations.	We request that the guidance propose the use of a risk based approach to determine relevant product contacting materials and critical components that should be identified.
439		The bullet calls for analysis of functional materials corrosion from the drug/biologic. This seems to imply that all materials be assessed for corrosion due to the drug/biologic. This is not necessary and only product contacting materials should be evaluated for corrosion due to the drug/biologic.	Please reword the bullet to read (added language in underlined font): Analysis of drug/biologic contacting functional materials corrosion from the drug/biologic product
D. Performance Testing: General Use Injector Considerations			
463		ISO 11608:2000 consists of 4 parts.	Please clarify if the reference in the draft guidance includes Parts 1-4 of ISO 11608:2000.
468		We are unaware of any ASTM standard with this title. In addition, the number is assigned to a different standard ("Standard Practice for Evaluating and Specifying Implantable Shunt Assemblies for Neurosurgical Application").	We recommend deleting reference to ASTM F647, Testing to Assess Durability of Devices Following Interaction with Drugs.

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476-479		The standards referenced for performance testing (lines 459-469) are recognized consensus standards and therefore if testing is performed in accordance with these standards, typical practice dictates that you can refer to the standard and not include detail around test set-up and methods.	Please clarify that details on test set-up and method should be provided only if recognized consensus standards are not used.
508		If there is any applicable ISO standard related to shelf-life stability and expiration dating that is relevant to general use injectors, please consider referencing it in the final guidance document.	Please reference any applicable ISO standard.
517		The three bullets (line 515-517) refer to shelf-life endpoints. It is clear how to test for freedom from defects and dose accuracy, but it is not clear how to test for replacement needles and cartridges. This needs to be clarified.	If it is FDA's intent to recommend testing for the functionality of the device after the maximum number of replacement needles and cartridges are used, then this should be included as a condition to consider when assessing the physical degradation and changes to the injector due to the conditions to which the injector is exposed during use (in-use life expiration dating), and should not be included as a shelf life-testing endpoint.

Line #	Criticality	Change Requested and Justification	Recommended Change
524-531		It is unclear what is meant by shelf life-testing endpoints for replacement needles and cartridges. This needs to be clarified (please see our comments immediately above).	Please edit sentence to read (additional language in underlined font): 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 the environmental conditions for intended use, or the environmental conditions defined in ISO 11608, such as the following:. Also, please delete "extreme" from line 529 and 530.
558		Functional evaluation of pressure and temperature conditions are covered by lines 524-533.	Delete "Structural testing at extreme pressure and temperature conditions", line 558.
E. Performance Testing: Injector and Drug/Biological Product Considerations			
584-585		Here the guidance mentions that additional pharmacology-toxicology testing may be appropriate depending on the specific materials in the product. This should be qualified by the appropriate use of risk assessments to evaluate risk associated with specific materials in the product.	We request that the guidance encourage use of risk assessments to evaluate risk associated with specific materials in the product and the need for pharmacology-toxicology testing. Examples of additional pharmacology/toxicology testing that may be appropriate would be helpful to clarify this point.
609		The requirement to ensure that each successive dose is the same as the first set dose does not apply to variable dose injectors that are designed to be able to deliver different doses.	Please edit sentence to read (additional language in underlined font): Testing to ensure that multi-dose cartridge injectors designed to deliver a set dose satisfy the requirement that each successive dose is the same as the first set dose.
614-617		Use of the specific drug/biologic product and the injector to determine dose accuracy seems excessive if the concern is with different	We suggest that the sentence be modified to state that: "Because diluents may affect dose accuracy of the drug/biological product in the injector, the testing described above should ensure that the delivery volume

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		diluents impacting dose accuracy.	meets the dose accuracy specification for the specific diluent used with the drug or biologic product."
625	High	The guidance fails to acknowledge that depth of needle penetration and dispersion of injectate are often well established for most needle-based delivery systems. The guidance should clarify that such requirements for testing should apply to novel delivery devices involving needle-free delivery systems.	We recommend the document propose a risk based approach to determining the need for testing in this section.
627-628		If a drug/biologic is used with an already approved injector with a defined needle depth, testing should be cross referenced to the appropriate submission containing that information.	Reword sentence to read (additional language in underlined font): Testing**,** or a cross reference to testing where appropriate, should demonstrate that the depth of needle penetration and/or dispersion…
628-629	High	There is no known model for stimulated skin testing. This would seem too burdensome and it is uncertain how this will be executed.	Please provide an example of a model that is appropriate for this type of testing or delete the requirement.
632-636		It seems overly burdensome to compare depth of penetration and dispersion testing of the subject injector with similar injectors or other methods of delivery, unless these devices are also included in the labeling for the product.	Please either delete this requirement or provide examples where applicable.
634-636	Medium	It seems unreasonable to request that statistical comparisons be done against similar injectors or other methods of delivery. Statistical comparisons with similar injectors or other methods of delivery are sometimes not feasible because of difficulty in obtaining competitor	We recommend deleting the sentence.

Line #	Criticality	Change Requested and Justification	Recommended Change
		products. It is uncertain why these data would be necessary and it seems unnecessarily burdensome. What is more important is that the drug-device combination products achieve the required delivery profile necessary for the drugs of interest.	
653-655		How population-specific issues may affect injection safety or effectiveness should be based on risk assessment rather than through human clinical studies.	We recommend rewording the bullet to read (additional language in underlined font): "Risk analysis on how population-specific issues, such as gender, body weight, age, and skin disorders, may affect injection safety or effectiveness."
662-697		Many of the requirements in the first 3 bullets under E.3 "Special Testing Considerations" section were previously addressed in section C "Injector Materials of Construction and Manufacture".	We recommend either removing the duplicative recommendations or providing more detailed cross references to Section 1.C.
686		Adhesion can also potentially change the delivered dose.	Please include "adhesion" in addition to "adsorption" since this has potential to change the delivered dose.
688-689		It is unclear how gases, liquids or solutes accumulate on a "surface of the drug/biological product". Does this mean accumulation on the surface of the injection device in which the drug/biologic product is contained?	Please clarify the sentence.
697		The link was found to be inoperative when access was attempted on July 16, 2009.	Please correct the link to the FDA Guidance "Container Closure Systems for Packaging Human Drugs and biologics: Chemistry, Manufacturing and Controls Documentation (May 1999), (http://www.fda.gov/cber/gdlns/cntanr.htm)).

Line #	Criticality	Change Requested and Justification	Recommended Change
709	Medium	Assessment of residual product and the impact of carryover should not need to be conducted for single use injectors / devices for which subsequent use would not be consistent with labeling, or perhaps even possible.	Please revise the sentence to state (additional language in underlined font): "For multiple use injectors, they should assess...."
713-720	High	Testing all stability and expiration dating tests with the entire injector system is unnecessarily burdensome. The guidance should allow manufacturers to use a risk based approach to determine which tests need to include the entire injector system and packaging.	We recommend rewording the sentence to read (additional language in underlined font): "Further, when conducting stability and expiration dating tests, a risk based approach should be applied to identify if the entire injector system should be tested…"
716-720		The draft guidance states: "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."	Please clarify whether the bench testing referred to in this section is to be done at the end of shelf life or as part of general design verification testing.
F. Performance Testing: Clinical Considerations			
747		It is unclear what is meant by "lock-out injectors."	Please provide further information to describe what is meant by the term "lock-out injectors."
G. Labeling			

Line #	Criticality	Change Requested and Justification	Recommended Change
Section 1.H		The elements to consider for inclusion in labeling cover the entire spectrum of injection delivery devices as well as combination products consisting of a drug or biologic product and a delivery device. It is not clear what specific type of labeling (Instructions for Use (IFU), Patient Package Insert (PI), other labeling) would be used to capture the requirements presented in this section. Without providing guidance on the type of labeling that should be used to capture this information it is of little value to the applicant. For example, labeling for a combination product would have information describing the proper handling and use of the device which could be included in an IFU document, while other information such as drug indication and safety information could be presented within a PI.	We recommend that the guidance reference established regulations and labeling guidance for drugs and devices and where appropriate due to potential risks to patients, distinguish labeling requirements for different classes of devices based on complexity and intended use.
827	High	Drug/biological products have labeling and instructions for use that provide information regarding the safe use of the product with the particular injector. Some of the elements listed will be in the approved labeling.	We suggest that the bullets referring to safety (lines 847 and 849) specify 'as related to the injector' as opposed to general contraindications and warnings.
827	Medium	Additionally, please consider requiring a cross-reference to the patient package insert or medication guide within the instructions if appropriate.	Please add cross-reference to the patient package insert or medication guide within the instructions if appropriate.

Line #	Criticality	Change Requested and Justification	Recommended Change
827	Low	It would be helpful to reference the information provided regarding visual inspection of the drug/biological product that is given at lines 349 to 366.	Please add visual inspection of the drug/biological product per lines 349 to 366.
827	Low	A reference to the *Guidance for Medical Device Patient Labeling* would be useful.	Please consider adding the following reference: *Guidance for Medical Device Patient Labeling; Final Guidance for Industry and FDA Reviewers (April 19, 2001)*
830-865		The draft guidance includes an exhaustive list of information to include within the patient labeling. This seems overly prescriptive yet lacking structure. The amount of information, level of detail and organization within the list make these recommendations difficult to follow.	Please consider removing specific labeling requirements unless they are pertinent to patient safety, in which case the requirements should be grouped into common buckets (*e.g.*, dosing, storing, safety, etc.) to enhance comprehension.
838	Medium	It is not clear why this bullet is included. Products can only have 'approved' labels in the market place.	We suggest deleting this bullet.
860	Medium	It is not clear why 'validation methods' would be included in labeling.	We suggest deleting this bullet.

APPENDIX 2:

EXAMPLE: Basic Requirements for a General Use, Electromechanical, Reusable Injector

I. INJECTOR CHARACTERISTICS:

1. Injector Type ☑ General ☐ Class ☐ Specific Product	**2. Usage** ☐ Single Use ☑ Re-usable ☐ Multi-use disposable	**3. Method of Administration** ☑ Needle ☐ Jet
4. Power Source ☐Mechanical ☑Electromechanical	**5. Dosage** ☐ Fixed Dose ☑ Variable Dose	**6. Single/Multiple Drugs Administered in Dose** ☐ Single Drug per dose ☑ Multiple Drugs per dose
7. Primary Drug Container ☐ Unchanged ☑ Changed		

II. RECOMMENDED REQUIREMENTS:

A. SCIENTIFIC AND TECHNICAL:

1. Identification	☑
2. Indication Information	☑
3. Conditions of Use	☑
4. Description of Drug/Biologic for Injection	☑

B. DESIGN FEATURES

1. Comparison to Existing Delivery Method	☑
2. Engineering Drawings and Photographs	☑
3. Dose Setting and Administering an Injection	☑
4. Graduation Marks and Fill Lines	☑
5. Visual inspection of the Drug/Biological Product	☑
6. Safety Features	☑
7. Human Factor Design Considerations	☑

C. INJECTOR MATERIALS OF CONSTRUCTION AND MANUFACTURE	☑

D. PERFORMANCE TESTING

1. Biocompatability	☑
2. Shelf-Life Stability and Expiration Dating	☑
3. Functional Testing	☑

E. PERFORMANCE TESTING: INJECTOR AND DRUG/BIOLOGICAL CONSIDERATIONS

1. Dose Accuracy	☑
2. Depth and Route of Injection	☑
3. Special Testing Considerations	☑
a. Extractability/Leachability	
b. Adsorptivity	
c. Drug/Biological Product Container and Closure Integrity	
d. Shelf Life Testing: Injector-Drug/Biological Product	

F. PERFORMANCE TESTING: CLINICAL CONSIDERATIONS

1. Human Factors	☑
2. Additional Considerations	☑

G. STERILIZATION AND STERILITY ASSURANCE

1. Sterilization	☑
2. Cross-Contamination Testing	☑

H. LABELING	☑

* *Note: Such a table could include more specific recommendations around different types of data that should be submitted in support a specific injector sub-type, rather than just section headings.*