



July 23, 2009

VIA ELECTRONIC SUBMISSION

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

Re: Comments on Draft Guidance for Industry and FDA Staff: Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products; Docket No. FDA-2009-D-0179

Dear Sir or Madam:

The Combination Products Coalition (“CPC”) is pleased to offer its comments on the *Draft Guidance for Industry and FDA Staff: Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products*. Policy development on combination products is necessary for these products to advance, and we are delighted to see the agency making progress in this area. Clearly, the draft guidance is the product of a tremendous amount of time and effort, and we would like to thank the agency for its thoughtful analysis.

By way of background, the CPC is a group of leading drug, biological product, and medical device manufacturers with substantial experience and interest in the combination products area. One of the principal goals of our organization is to work with the agency on issues affecting combination products, in order to advance our common missions of providing the best possible health care for patients. Because of our diverse, cross-industry membership, we think the CPC brings a broad and unique perspective to issues affecting combination products.

Below, we offer our general and specific comments on the draft guidance. For clarity, we often refer to the line-numbered version of the draft guidance. Overall, we believe the document will require significant revisions in order to provide useful guidance to regulated industry and FDA personnel.

Executive Summary

We are pleased that the agency issued the draft guidance in order to advance discussion regarding injector product submissions. We hope that the agency will carefully consider the comments it receives in developing a final guidance document. As explained in more detail below, we have several major concerns with the draft guidance, including:

1. It does not provide adequate information on specific injector types. Rather, the document sets forth catch-all lists that encompass any and all injector types. This is a fundamental problem that severely impedes the guidance's usefulness.
2. It fails to address several fundamental issues impacting injector product submissions, including the number and type(s) of initial submissions, modifications to approved products, and clinical trial issues.
3. The scope of the definition of "injector" merits additional discussion. Such additional information is imperative to understanding the scope and effect of the guidance.
4. The draft guidance has confusing language throughout that needs to be clarified.

Below we explain these and other concerns in more detail.

General Comments

I. FDA should redesign the draft guidance to describe regulatory pathways for specific types of injector products.

Our fundamental concern is that the draft guidance fails to help its intended audience (industry and FDA personnel) understand how to get injector products to market in a compliant, least burdensome manner. More specifically, the current draft consists primarily of catch-all lists of data recommendations and considerations that might apply to any given technology; it contains little in the way of guidance for specific injector types. From our view, this content is simply not helpful in light of the wide range of injector technologies and products. Ultimately, we believe the draft guidance should be completely restructured to address specific types of injector products.

Below we elaborate on these keys points by applying a rhetorical device we find helpful in analyzing any guidance, but especially this one. Please indulge us in this analogy for a moment: we think you will find it helpful too.

a. An analogy: Good Guidance Practices are similar in function and form to a quality system.

A robust quality system is important for ensuring the quality, safety, and integrity of drugs, biological products, and devices. In a similar fashion, the agency’s Good Guidance Practices (“GGPs”) are meant to ensure the agency issues quality guidance that achieves the guidance document’s stated purposes.

Taking our analogy a step further: design controls as an element of a quality system ensure that a product meets its specified design requirements. Generally speaking, design controls provide this assurance through various steps, and each of those steps has a counterpart in the guidance development process:

Quality System Design Controls	Guidance Development Processes
1. Design and development planning	Decision-making on the need for guidance
2. Design input, including assessing the user requirements	Identifying the needs of the intended audience, including the agency and the industry if both are intended
3. Design output	First draft of the guidance
4. Design review	Comment opportunity
5. Design verification and validation	Testing the final draft by allowing agency leadership to review through the prism of the comments

If we think of guidance document development in these design control terms, the guidance document is actually the ultimate product of a long, rigorous process involving various input, output, and review stages. More specifically, the design input would be the needs of the intended guidance users (here, according to the agency’s statement of intent, FDA staff and industry), and the initial design output could be considered a draft guidance. Design review could be considered what we are doing now – analyzing whether the design output satisfies design input. It does not.

b. Here is our biggest concern: The “Design Output” (i.e. the draft guidance) does not meet user needs.

i. Industry users need guidance on the least burdensome regulatory pathways for specific injector products.

As you know, injectors intended for use with drugs and biological products are of particular importance and benefit to patients and their caregivers. While these technologies hold great potential, they also present significant regulatory challenges as industry struggles to understand how to get the products to market in a compliant, least burdensome manner. Thus,

industry's need, which is a design input for the draft guidance, is for guidance on least burdensome pathways to market for specific types of injectors.

There has been some debate about the extent to which the least burdensome concepts apply to combination products incorporating a device constituent part. Therefore, we are pleased that the guidance recognizes the application of the least burdensome principles.¹ Those least burdensome principles require that information unnecessary to a regulatory decision should not be part of the decision-making process, and that all reasonable measures should be used to reduce review times and render regulatory decisions within statutory timeframes.² These are additional elements of the design input for the draft guidance.

ii. The Design Output (i.e. the draft guidance) is a comprehensive, catch-all list of requirements largely unconnected to any type of injector.

The guidance applies to a broad array of injectors. In particular, the definition of “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 definition covers a wide range of technologically-diverse injectors – from relatively simple piston syringes, to far more complex computerized injectors. The draft guidance also covers both stand-alone, general use device injectors, as well as injectors that are a constituent part of a combination product.

Despite this wide breath of scope, the draft guidance does little to differentiate among the requirements that may apply to different types of injectors. Instead, it lumps together the scientific and technical considerations that may or may not be relevant depending upon the type of injector at issue. It appears as though the agency analyzed numerous types of injector applications/submissions and compiled comprehensive lists of the data that could apply to injectors. The guidance then provides a comprehensive list, but the connection to the specific type of injector has been lost.

An illustration may help to clarify this important point. In the figure below, we use letters A through N to denote generic data requirements.

¹ FDA, *Draft Guidance for Industry and FDA Staff: Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products*, at 5 (April 2009) (“Draft Guidance”).

² FDA, *The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles; Final Guidance for FDA and Industry* (Oct. 4, 2002) (“Least Burdensome Guidance”).

When all the information gets collapsed to the bottom line, much is lost.

Injector Type	Potential Data Requirements and Considerations													
	A	B	C	D	E	F	G	H	I	J	K	L	M	N
Piston Syringe	✓	✓	✓											
General use pen injector	✓	✓		✓	✓	✓	✓							
Pen injector approved for use with Drug X	✓	✓				✓	✓	✓	✓					
Needle-free injector approved for use with Drugs X, Y, and Z	✓	✓			✓			✓	✓	✓	✓	✓	✓	✓
Draft Guidance: All Injectors Together	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

The draft guidance focuses on providing the information in the white area at the bottom—the scientific and technical considerations that may apply to any injector, *of whatever type*. More specifically, in several instances, the guidance provides a lengthy list of all possible issues that the agency might consider, or data that the agency might recommend, rather than specific guidance and direction on scientific and technical information associated with specific types of injectors. *In this way, the guidance becomes a mere laundry list of data requirements and considerations that might apply to a given technology—from our viewpoint not at all a useful output.*

A far more useful approach – and one that meets industry’s need for guidance – would entail teasing apart these comprehensive, catch-all lists into specific pathways for market for specific types of injectors that have comparable features, as is illustrated by the darkened area in the figure above.³

c. The current Design Output (i.e. draft guidance) results in an overly burdensome, confusing document that could delay needed technologies.

Importantly, the current structure of the draft guidance has several potential problematic consequences. One major consequence of the current draft is a significant increase in the

³ We recognize there may be multiple pathways to market. In such cases, we believe the guidance should set forth the possible alternatives.

regulatory burdens associated with applications for general use injectors and for NDA/BLA applications under which an injector is approved. Another key example of how the guidance seems to increase regulatory burden is the way in which it is inconsistent with other FDA guidance documents, for example, with FDA’s *Guidance on the Content of Premarket Notification (510(k)) Submissions for Piston Syringes*. The table below summarizes the major categories of inconsistencies:

	Current Piston Syringe Guidance Element	Draft Guidance Element
Scope	Applies to (empty) piston syringes, cartridge and pen syringes, accessory devices such as dispensing pens and syringe holders; Excludes prefilled syringes that are the subject of NDA or BLA approvals.	Applies to a wide array of injectors, including jet injectors (fluid injectors), pen injectors, piston syringes, needle-free injectors, mechanically operated injectors; Includes prefilled and non prefilled syringes.
Overall structure/ information provided	Provides guidance on presentation of data, data analysis, and other issues; Guidance is specifically directed to piston syringes.	Provides very specific, detailed guidance on presentation of data, data analysis, and other issues; however, this detailed guidance is not specific to any injector type.
Performance data; use of standards	Allows provision of data or certification with a standard, which allows the applicant to exclude data presentation.	No data exclusion based on reference to a standard. In addition to submission of data, requires detailed description of test set-up and explanation of how each test was conducted.
Device description; design features	Provides guidance on general design features relevant to the use of a device alone and the device used with a specific drug or biologic, specifically: type, drawing, intended use, and physical, mechanical, biological, and chemical specifications.	Sets forth specific, detailed recommendations for design features associated with the many types of injectors included in the guidance, in addition to specific information about the drug or biologic to be used with the device, for example: detailed comparison to existing delivery method (indication for use, conditions of use, injection site, depth of needle insertion, injector life, compatibility cartridges and needles, etc), engineering drawings and photographs, dose setting and administering and injection, graduation marks and fill lines, visual inspection of the drug/biological product, safety features, and human factor design considerations.
Performance testing	Provides general guidance on: Biocompatibility, comparative claims, unique designs, drug/biologic and device	Sets forth specific guidance that is categorized at a high level by the type of injector and indication for use:

	Current Piston Syringe Guidance Element	Draft Guidance Element
	compatibility, drug/biologic stability.	<u>General Use:</u> Biocompatibility, shelf-life stability and expiration dating, functional testing <u>Injector and Drug/Biological Product:</u> Dose accuracy, depth and route of injection, extractability/leachability, adsorptivity, container closure integrity <u>Clinical considerations:</u> Mention of clinical studies, human factors
Biocompatibility	Reference to ISO 10993 and relevant ASTM standards.	Reference to ISO 10993 and additional specific recommendations for extraction testing and justifications.
Labeling	Provides general direction on labeling sufficient to describe the device, its intended use, and the directions for use.	Sets forth specific recommendations for instructions, diagrams, warnings, contraindications, claims, environmental conditions, reuse, cleaning, troubleshooting, life of injector and critical components and additional drug/biologic specific instructions.

We suspect that these inconsistencies have arisen because the guidance does not differentiate among the data requirements that may apply to different types of injectors. However, if the agency truly intends to increase regulatory requirements associated with these comparatively simpler devices, this seems to violate least burdensome principles in that existing, less burdensome approaches for general use, stand-alone injectors seem to be working well for the agency and stakeholders.

Below in our specific comments (Part III), we provide several more examples of instances in which we believe the draft guidance exceeds necessary requirements.

As a result of these overly burdensome and confusing recommendations, injector applicants – particularly those who are inexperienced and thus perhaps most in need of guidance – are very likely to err substantially on the side of over-inclusiveness in their injector submission. Such an approach is inefficient for both the agency and stakeholders and ultimately harms patients by delaying access to new technologies.

d. The guidance should be restructured to describe regulatory pathways for specific categories of products.

For the reasons above, we are concerned that unless the draft guidance is substantially restructured, it cannot meet required least burdensome principles and will fail to meet its stated

objective of streamlining the review process. Ultimately, in order to provide useful, least burdensome guidance to stakeholders, the guidance should clearly distinguish among the various regulatory categories of injectors and should delineate the various least burdensome pathways to market for specific injector types. Further, in developing a final guidance, we recommend that the agency more comprehensively address related guidance documents and help industry understand how these apply in the future, or whether they are replaced or superseded. We believe that this step will help ensure consistent guidance for combination products across agency Centers.

II. The guidance should address additional issues pertaining to injectors and products incorporating injectors.

The draft guidance fails to address a number of policy issues on which stakeholders need guidance. We believe that a revised guidance should address each topic that meets the following three criteria:

1. The issue is within the natural scope of the guidance, considering how issues are naturally intertwined, where one cannot really be resolved without the other.
2. The issue is important to address – in other words, going back to our discussion of design input, the intended users of the guidance need guidance on the particular issue.
3. There is ambiguity surrounding the issue.

In addition to the topics currently addressed in the draft guidance, we believe the following areas as they relate to injectors should be addressed in the final version of the guidance. Each of these topics meets the first criteria because they directly concern injectors and are intertwined with the issues the draft guidance addresses. While a few of the topics address post-market compliance issues, we believe these are relevant and needed areas for guidance. In this regard, we believe that the second criteria is also met, because industry (if not also FDA staff) have a need for guidance on the issues proposed below in order to get new products to market and monitor them appropriately. Finally, as noted below with regard to each issue, there is ambiguity on each of these topics.

- Submissions - Although the draft guidance is primarily focused on data requirements for market applications, it omits discussion of certain key, intertwined issues regarding submissions. There is ambiguity on these issues as they apply to combination products incorporating injectors. Specifically:
 - o The guidance states that considerations for determining the appropriate type of marketing application are beyond the scope of the guidance. However, because flexibility in marketing applications can have an important impact on the pace of future product development and on the overall availability of combination products for patients, the guidance should acknowledge the fundamental

principles described in the CPC's comments on the OCP's Concept Paper on the Number of Marketing Applications for a Combination Product.⁴ In particular, sponsors of combination products should have primary responsibility for deciding and justifying how many applications to file for a given combination product. FDA will review these proposals and respect a sponsor's decisions about the number and type(s) of applications, as long as the proposal is consistent with applicable law. The agency has not responded to our and other stakeholders' comments on the Concept Paper; does FDA agree with this concept as applied to injectors?

- Further, how do data requirements vary based on approval status of the drug or biological product and the injector? In other words, when do applicants have different or more rigorous data requirements when a constituent product of the combination product is not yet approved for marketing? Examples of stages/product status for injector implementation include:
 - Unapproved drug product/Unapproved injector
 - Unapproved drug product/approved injector
 - Approved Drug/New Primary Container/Closure/Unapproved injector
 - Approved Drug/New Primary Container/Closure/Approved injector
 - Approved Drug in Primary Container/Closure/Unapproved injector
 - Approved Drug in Primary Container/Closure/Approved injector
- When must data be submitted versus summarized in an application?
- Although the guidance touches on referencing Device Master Files (see lines 219 – 230), we believe the guidance should be broadened to address drug and biologic master files. Was the omission of drug and biological master files intentional? If so, does the agency believe that device, drug, and biological master files should be used in significantly different manners?
- *Device Modifications* - The draft guidance does not address the rules pertaining to device modifications, including any needed FDA submissions. Because guidance for combination products on this issue is limited, manufacturers of combination products incorporating injectors have struggled with these ambiguities. In particular:
 - Parameters for analyzing modifications to the injector constituent part of combination products approved under a single NDA or BLA – what rules does the applicant use when deciding whether to submit an update or an application for a device modification? Often the drug rules don't make sense for device changes.

⁴ The CPC's comments are available at: http://combinationproducts.com/images/Comments_FDA_111505.pdf.

- Parameters for analyzing modifications for other types of combination products incorporating an injector constituent part, i.e., cross-labeled and kit products. Again, what rules apply, particularly when there are multiple applications?

We believe that addressing the above issues would help to provide a more comprehensive and useful guidance for both agency personnel and industry.

Below we offer more specific suggestions on the content of the guidance.

Specific Comments

III. The draft guidance does not meet industry's need for least burdensome guidance on specific injector types.

Above we explained that industry needs guidance on specific injector types that addresses how to get injector technologies on the market in a compliant and least burdensome manner. The current draft of the guidance does not meet this need because it merely provides catch-all lists of information that are unconnected to any specific types of injectors. In several instances, this structure has resulted in confusing and unnecessarily burdensome recommendations. Here are several examples of instances in which we believe the guidance exceeds necessary requirements:

- Line 115: The guidance says that a submission will typically include, among other things, the device regulatory classification and product code. In our experience, an NDA or BLA often would not include such information.
- Line 120: The inclusion of “demographics” in a proposed indication statement goes beyond current accepted requirements.
- Line 131: The guidance says that a submission will typically include the “drug/biological product(s) of intended delivery” in a submission. In our experience, such information would be appropriate for an NDA or BLA, but not for a 510(k) submission.
- Lines 165 – 185: These recommendations are excessive for simple devices, such as piston syringes, and even appear to reflect worst case scenario for more complex devices. More specifically:
 - A general use device applicant is unlikely to have the information set forth in lines 174 – 179 for all drugs and biological products compatible with the injector. A more appropriate focus is on the injector materials and suitability for use under a range of conditions typical for the drug or biological product.

- With respect to lines 181 – 185, we are unclear how a device applicant could address these recommendations, as a device applicant is unlikely to know of development plans or submissions under review unless the applicant is partnered with a specific drug company. We are also unclear of the purpose of such contacts to CDRH or to the OCP.
- Lines 192 – 202: These requirements also seem far beyond current expectations.
- Lines 253 – 271: The guidance implies that all the information listed here should be included as required design features for all injectors. The guidance should allow for a risk based approach to applying requirements to specific devices and should be more specific on what information applies to specific types of injectors. It would also be helpful to delineate expectations for data that should be included in master files, versus elements that should be included in the actual NDA/BLA marketing application.
- Lines 274 - 275: The guidance implies that an NDA or BLA seeking approval of an injector should compare that injector to other legally marketed products. In our members' experience, such an approach would be unprecedented; examples would be helpful here.
- Lines 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 itself developed the injector device.
- Lines 298 – 366: Again, 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 personnel are clear on information a submission should include.
- Lines 408 – 415: This recommendation for all known materials comprising the injector and all manufacturing materials goes far beyond current expectations.
- Lines 430 – 441: The guidance implies that the full list of these issues should be addressed in all injector submissions. However, this list seems to reflect issues to consider when the injector is in contact with the drug or biological product.
- Lines 459 – 469: The testing requirements in one or more of these referenced standards may not apply to all situations. The guidance should acknowledge this possibility.
- Lines 476 – 478: The standards referenced for performance testing (lines 459-469) are recognized consensus standards. Therefore, if testing is performed in accordance with these standards, typical practice dictates that an applicant may

refer to the standard and not include detail on test set-up and methods. The guidance should clarify that details on test set-up and methods should be provided only if recognized consensus standards are not used.

- Lines 584 – 585: Here the guidance states that additional pharmacology-toxicology testing may be appropriate for a submission. This seems overly burdensome, and we ask that the agency provide examples so we can better understand this possibility.
- Lines 510 – 539: Here is another example of where guidance on specific injector types and stages would be useful, for example, pre-filled syringes prior to filling.
- Lines 614 – 617: In our experience, use of the specific drug/biologic product and the injector to determine dose accuracy is excessive if the concern is with different diluents impacting dose accuracy. We suggest that this sentence be modified as follows: “Because diluents may affect dose accuracy of the drug/biological product in the injector, the above testing should ensure that the delivery volume meets the dose accuracy specification **for the specific diluent used with the drug or biologic product.**”
- Lines 625 – 660: The guidance fails to acknowledge that depth of needle penetration and dispersion of injectate are often well-established for most needle-based delivery systems and indeed are more controlled than the same injections done manually. The guidance should clarify that such requirements for testing should apply to novel delivery devices involving needle free delivery systems. Further, the guidance should recognize that if an NDA/BLA refers to an already-approved injector with a defined needle depth, the application may cross reference the applicable testing in the approved submission.
- Lines 632 – 634: 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. The guidance should either clarify where such information would add value or delete this sentence.
- Lines 634 – 636: Conducting statistical comparisons against similar injectors or other methods of delivery is unnecessarily burdensome. This sentence should be deleted.
- Lines 713 – 720: 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 define which tests need to include the entire injector system and packaging.
- Lines 818 – 870 (Section I.H): The elements the guidance lists for consideration in regard to labeling cover the entire spectrum of injectors. Further, we are also unclear on which type of labeling (for example, Instructions for Use, package insert, other labeling) would include the elements presented in this section.

Without any connection to injector or labeling type, this information is of little use.

IV. The draft guidance should clarify and provide more detail on the definition of “injector” and the impact of specific injector features.

As mentioned above, the draft guidance’s definition of injectors is very broad. We believe the final guidance should clarify key aspects of this definition, in particular:

- Scope of injector definition

- The way in which “injector” is defined – as including (but not limited to) jet injectors, pen injectors, piston syringes, needle-free injectors, mechanically operated injectors, and injectors with computerized or electronic elements – encompasses several types of technologically-diverse injectors. As discussed above, the agency has already issued guidance on piston syringes. We believe the draft guidance should clarify that it is intended to apply to autoinjectors and should define that term accordingly, excluding manual injectors from its scope. Further, we believe that the title of the draft guidance should include the term “autoinjector” (whether the scope is narrowed or not), to ensure that interested parties may locate the guidance when searching electronically.
- As mentioned above, the definition of injector “is not limited to” the types of injectors that the draft guidance specifically lists. Clarification on what other types of injectors the agency believes are included would be helpful.
- The draft guidance mentions some injectors that are excluded from the document’s scope, such as dental surgery jet injectors.⁵ The guidance should explain why these injectors were excluded, as such rationale can be useful in assessing whether the guidance applies to other injector types. Additionally, it would be helpful to understand whether any other products may be excluded. For example, does the scope of the draft guidance include pumps? Some discussion in the draft guidance (e.g., discussion of flow rate) suggests that infusion pumps are included.

- “Product class” and “product line” -- The draft guidance uses the terms “product class” and “product line” in defining groups of injectors and references these terms throughout the draft guidance in relation to specific requirements. We are unclear on what these terms mean in relation to injectors. We ask that the agency consider whether it is more appropriate to delineate basic groups of injectors into two main groups: (1) general use injectors; and (2) injectors that are part of a combination product. At a minimum, the guidance should provide examples of “product class” and “product line” in the context of injector products.

⁵ Draft Guidance at 4.

We believe these clarifications would help industry and FDA staff better understand how the draft guidance may be applied to specific products and applications.

Above we discussed our overarching concerns with the structure of the draft guidance in light of its broad scope, stating our view that the draft guidance should be refined to describe specific regulatory pathways (and their alternatives) for specific types of injector products. In addition to this overall restructuring, we believe the draft guidance should specifically address how a number of defining characteristics about injectors may impact their regulatory status. These issues include:

- *Impact of injector features*

Such features include:

- Differences in requirements for products incorporating syringe-based injectors versus cartridge-based injectors
 - The role and impact of automation, including:
 - Injection
 - Needle insertion
 - Needle shielding
 - Any other automated functions
 - Single injection versus supporting multiple injections
 - Fixed dose versus supporting variable doses
 - Spring-containing
 - Platforms intended for use with multiple drugs
 - Relevance of 21 CFR 880.6920 (device classification for syringe needle introducer), including how FDA differentiates among spring-containing needle introducers, injection pens, and injectors
- *Type of combination product* – Finally, we believe it is of particular importance to understand how designation as a single entity, kit, or cross-labeled combination product impacts applicable regulatory obligations for combination products incorporating an injector. In this regard, it would be helpful for the guidance to address when an injector is or becomes a combination product and provide examples of single entity, kit, and cross-labeled injector combination products.

V. The draft guidance should clarify issues pertaining to the number and types of marketing submissions.

Above we discussed the broader policy issues that we believe the draft guidance should address in the context of marketing submissions for injectors or combination products that incorporate an injector constituent part. In addition, although the guidance states that considerations for determining the appropriate type of marketing application are beyond the scope of the guidance, it nevertheless makes sweeping statements on this topic (see lines 78 – 90). We believe elaboration and clarification is warranted in several important respects, as follows:

- Line 81: The guidance says that general use injectors “typically” have market clearances as devices under 510(k) submissions. The guidance should describe and provide examples of exceptions to this general statement.
- Lines 82 – 85: The guidance makes reference to injectors intended for use with a specific drug/biological product that are pre-filled with that product, co-packaged with that product, or separately provided with mutually conforming labeling. The guidance goes on to say that these are “typically” combination products under 21 CFR 3.2(e). The guidance should describe and provide examples of exceptions to this general statement.
- Lines 87 – 89: The guidance states that in some situations, FDA may determine that two applications are necessary for a combination product incorporating an injector. We believe the guidance should provide examples of such a scenario.

As currently drafted, the guidance brings up the important issue of marketing submissions, yet asserts that the issue is beyond the guidance document’s scope. Because the current language raises important questions about the number(s) and type(s) of submissions, we believe that the agency should revise this section to provide much-needed clarification on its stated recommendations.

VI. The draft guidance should address how requirements for clinical data may differ depending upon the type of injector at issue.

Although the draft guidance addresses the important topic of clinical studies, it does so in a summary fashion and, again, does not sufficiently acknowledge differences among different injector types.

For example, the draft guidance implies that there should be a clinical study for all types of injectors. Of course this is not the case, particularly with stand-alone, general use injectors. In this regard, we believe the draft guidance should specify and clarify instances in which FDA believes clinical data are needed. Conversely, the draft guidance also should acknowledge instances in which studies are not required and in which simulated use studies are preferable. Illustrative examples would be particularly helpful here.

We also believe that the topic of clinical trial design merits more discussion. On the one hand, the draft guidance says that specific considerations for clinical trial design are outside of its scope. Yet the draft guidance raises important trial design issues by making the sweeping statement that generally “clinical trials for some injectors may focus on the injector itself.” We are unclear on what the draft guidance means here and believe examples would be very helpful to illustrate the agency’s point.

VII. The draft guidance should clarify several instances of confusing language throughout the document.

In addition to the above issues, in reviewing the draft guidance, our members identified a number of confusing areas that warrant clarification. These issues are as follows:

- Lines 19 - 21: We are unclear whether the reference to 510(k)s or PMAs 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. This could be easily clarified by replacing the term “injector alone” with “general use injector.”
- Lines 21 – 23: Because the type of filing associated with a combination product is determined by the product’s primary mode of action, the guidance should clarify that typically an NDA or BLA is the marketing application **when the primary mode of action is the drug or biologic.**
- Line 123: We are unclear what is meant by “target tissue characteristics.” Does this refer to injections delivered subcutaneously, intradermally, or intramuscularly?
- Lines 275-277: The guidance implies that an NDA/BLA reference may need a letter of authorization to reference another applicant’s 510(k). However, while a letter of authorization is needed to reference the proprietary information in a master file, such an authorization is not necessary to reference information in a 510(k). Further, obtaining a letter of authorization can be impractical in instances where there is not cooperation between the NDA/BLA holder and the 510(k) holder. The draft guidance should clarify this distinction.
- Line 279: We are unclear why the guidance includes “(risk)” in this sentence. This should be deleted.
- Lines 336 – 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 may serve other purposes, such as a check to ensure there was no leakage of product during shipping. In such cases, fill lines may be placed after the product is filled, and validating the accuracy of the marketing is not necessary. Therefore, we believe lines 346 – 347 should be clarified as follows: “When

using graduation marks or fill lines **to aid the user in setting the correct dose or for verifying the set dose**, the submission should include validation...”


- Line 453: Here the guidance references testing with “alternative substances.” We are unclear on what this term means. Examples would be helpful.
- Line 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 believe this reference should be deleted.
- Line 517: We are unclear on what the agency means by shelf life-testing endpoints for replacement needles and cartridges. This needs to be clarified. However, if the intent is to test for the functionality of the device after the maximum number of replacement needles and cartridges are used, such testing is more appropriately considered as a condition for assessing the physical degradation and changes to the injector due to the conditions the injector is exposed to during use (in-use life expiration dating), rather than a shelf life-testing endpoint.
- Lines 524 – 526; 529 – 530: We are unclear on what the agency means by “extreme” in reference to operating/storage temperatures and conditions of use. A more appropriate reference would align either with the worst case that the device will likely be subject to or with defined conditions in ISO 11608. In particular, we suggest that the sentence in lines 524 – 526 be edited as follows: “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 **for intended use, or the environmental conditions defined in ISO 11608**, such as the following ...” Also, the word “extreme” should be deleted from lines 529 and 530.
- Line 558: Functional evaluation at extreme pressure and temperature conditions are covered by lines 524-533. The bullet at line 558 should be deleted.
- Line 588 – 590: This reference to biocompatibility testing is confusing in that such testing would typically not be performed with the drug. We ask that the agency clarify this statement.
- Line 598: We believe the agency should clarify whether “adherence” should instead say “absorption.”
- Lines 609 – 610: 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. We recommend that this sentence be clarified as follows: “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.”

- Line 655: The guidance should clarify what it means by testing to examine “the presence of blood vessels.”
- Lines 662 – 697: Many of the recommendations for testing in this section are addressed in the prior Section I.C (Injector Materials of Construction and Manufacture). We suggest that the guidance either remove the duplicative recommendations or provide more detailed cross-references to Section I.C. Further, within this section at lines 688 – 689, we are unclear how gases, liquids or solutes accumulate on a “surface of the drug/biological product.”

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We are pleased that the agency issued this draft guidance for discussion. Tackling such a guidance – particularly one on a topic as complex and far-reaching as the regulation of injectors – is not an easy task. Because of the important implications of this draft guidance, we urge the agency to carefully consider stakeholder and internal comments as it finalizes the guidance. We are happy to help in any way we can. Please do not hesitate to contact me using the information below.

Respectfully submitted,



Bradley Merrill Thompson,
On behalf of the Combination Products Coalition

bthompson@ebglaw.com

Phone: 202-861-1817

Fax: 202-861-3517