Combination Products Coalition

1227 25th St. NW #700
Washington, DC 20037
combinationproducts.com
202.861.1881

July 9, 2013

VIA ELECTRONIC SUBMISSION

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

Re: Docket No. FDA-2013-D-0362: Comments to FDA Guidance: Glass Syringes for Delivering Drug and Biological Products - Technical Information to Supplement International Organization for Standardization (ISO) Standard 11040-4.

Dear Sir or Madam:

The Combination Products Coalition ("CPC") is pleased to offer its comments on the Draft Guidance for Industry and FDA Staff: *Glass Syringes for Delivering Drug and Biological Products - Technical Information to Supplement International Organization for Standardization (ISO) Standard 11040-4* (hereinafter "Draft Guidance").

By way of background, the CPC is a diverse group of drug, biologic, and medical device manufacturers with substantial experience in the combination products area. Our members range in size from small start-ups to multibillion dollar manufacturers. These companies all share an intense interest in policy issues affecting combination products. Because of our diverse, cross-industry membership, we think the CPC brings a broad and unique perspective to issues affecting combination products.

Overall, we are quite pleased that FDA has drafted this guidance in response to the Safety Alerts advising the industry of adverse events and product quality concerns related to connectivity issues with certain glass syringes. Given that such complications could delay the administration of medication in emergency situations potentially resulting in serious harm to patients, manufacturers want to ensure that such issues do not occur and thus appreciate the need to supplement ISO-110404-4.

However, the Draft Guidance raises a number of important concerns. First, the Draft Guidance is unclear whether it applies to already marketed products or whether it only applies to products in development. Second, some tests recommended in the Draft Guidance do not appear to be related to connectivity issues; it is therefore unclear how these tests fit in a guidance concerning ISO 11040-4. Finally, the Draft Guidance also seems to indicate that only glass prefillable syringes are the cause of the connection issues as it makes no reference difficulties caused by certain needleless luer access devices ("NLADs"), many of which have luer shapes and/or thread designs that do not conform to the ISO 594 Standard.

Below we provide our comments and recommendations in more detail which we believe will improve the clarity of the Draft Guidance:

1. **FDA should clarify that this guidance applies only to products that have not already been cleared or approved, unless such products are undergoing significant changes requiring a new 510(k) or a PMA.**

It is unclear as to whether manufacturers should consider the Draft Guidance for planned submissions moving forward or whether manufacturers should also apply it to their already cleared or approved products. The Draft Guidance states that glass syringes that demonstrate conformity with the ISO 11040-4 standard alone does not ensure that the glass syringe can be properly connected to connecting devices such as needles, needleless luer connectors, adapters, and transfer units. Therefore, FDA has recommended that supplemental tests be conducted for parameters beyond those mentioned in ISO 11040-4, to demonstrate that the glass syringe has interoperability with connecting devices so that proper delivery of drugs and biologics can occur. However, the guidance does not mention whether these supplemental tests must be conducted on already-marketed products that pose no safety or product quality issues.

In addition, the Draft Guidance has recommended design or re-design options that are listed in Subsection A and that this guidance applies to all sponsors of an IDE, HDE, 510(k), or PMA, and to the sponsors of an IND, BLA, NDA, or ANDA for a drug or biologic that is delivered with a glass syringe. Here again, there is no clarity as to whether FDA is recommending that manufacturers consider re-designing all existing products that have been cleared or approved and pose no safety or quality issue.

CPC recommends that FDA clarify that manufacturers are not required to conduct supplemental tests on all *already-marketed products*. Manufacturers that have already obtained clearance, or in some cases approval, for their products may have adequately demonstrated that their product poses no connectivity issues, in other ways not described in this guidance. For an example, a manufacturer may have taken into consideration the key dimensions ISO 11040-4 seems to lack (e.g. dimensions for the glass syringe nozzle internal diameter, thickness of nozzle wall, and barrel neck curvature) or other dimensions FDA recommends such as the height of the nozzle for a glass barrel syringe intended to connect to a luer lock fitting or dimensions that would accommodate luer locks with a center pin piercing element. CPC does however agree that, to the extent a product that has already been cleared or approved is undergoing a change, manufacturers should determine if the recommendations in this guidance apply to such changes.

We request that FDA clarify, that the recommendations in the guidance only applies to products with forthcoming submissions, such as products in development or already-marketed products undergoing significant changes requiring a new 510(k) or PMA.

2. **FDA should remove any recommendations that are not specific to the connectivity issue the guidance is intended to address**

The additional considerations recommended in Section V of the Draft Guidance do not appear to relate to connectivity issues that the Draft Guidance was intended to address. Rather, they appear to provide vague general guidance on requirements for glass syringe submissions. For example, Section V.B.8. of the Draft Guidance recommends that testing of a combination product containing lyophilized drug/biologic and diluent should address, among others, the ability of the delivery system to exclude drug/biologic-diluent contact during storage and

shipment,. It is unclear as to why such an analysis was included in this Draft Guidance because there is no explanation on how such an analysis would relate to the connectivity issues sought to be addressed by the Guidance.

Given these ambiguities, the CPC urges that any final guidance include only the supplemental data that are needed to address the connectivity issues that resulted from the gaps in ISO-11040.

3. **FDA should address the connectability issues that are due to luer access devices that do not meet the design specifications of ISO 594-1 and 594-2 Standards.**

A number of luer connector devices have male and female luer designs that do not meet the design specifications of the ISO 594-1 and 594-2 Standards. In many cases, these products were designed to be used with disposable plastic syringes and contain a "center pin." which is intended to enter the lumen of the syringe luer and the fluid is transferred through that center pin. This "center pin" design for needleless connectors is a radical departure from the standard luer design and is not defined or taken into account in any luer standard. Although these devices work well with disposable plastic syringes that have a large lumen, they do not work with most glass prefillable syringes as most have a small lumen that will not allow the center post to enter the space. Thus, when clinicians attempt to connect a glass prefilled syringe to an NLAD with a center pin, the center pin may break preventing the clinician from delivering the drug. Because these NLADs work with disposable plastic syringes, the clinician may believe that the cause of the problem was that the glass luer broke as they are unaware that the NLAD has a center post.

Although we concur that conformance to ISO 11040-4 by glass prefillable syringes alone will not ensure eliminate all connection issues and ensure compatibility with all connectors on the market, the Agency also should address the role that connectors design plays in the connection issues discussed in the Draft Guidance. The Agency should take steps to ensure that all new luer connector devices comply with the existing ISO luer standards, especially the new ISO 80369 Standard once it is issued, demonstrate the ability to connect to all syringes on the market, or contain labeling statements regarding syringes with which they are not compatible.

* * *

We appreciate the opportunity to comment on the Draft Guidance and hope these comments will allow the Agency to clarify these points in any final guidance that is published.

Kindest regards,

Bradley Merrill Thompson,
On behalf of the Combination Products Coalition