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

Reference: FDA Draft Guidance Glass Syringes for Delivering Drug and Biological Products: Technical Information To Supplement ISO Standard 11040-4

Dear Sir/Madam,

PDA recognizes the potential risk to patient safety as a result of connectivity problems between prefilled needleless glass syringes and pin activated needle free connecting devices and appreciates FDAs efforts to address the risk with this draft guidance.

PDA is not aware of a more general issue affecting connectivity between syringes conforming to ISO 11040-4 and standardized ISO 594-2 conical Luer Lock fittings. Therefore, PDA recommends that FDA limit the scope of this guidance document to the more specific topic of connectivity with pin activated needle free connecting devices and that the guidance strike a balance between modifying the syringe tip to fit the pin activated needle free connecting devices and modifying the pin activated needle free connecting devices to fit the syringe. The attached comments and proposed changes were developed to focus the guidance on this specific patient safety concern.

PDA is a non-profit international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical, biological, and device manufacturing and quality. Our comments were prepared by a committee of experts with experience in pharmaceutical manufacturing including members representing our Board of Directors and our Regulatory Affairs and Quality Advisory Board.

If there are any questions, please do not hesitate to contact me.

Sincerely,

Richard Levy,
Senior Vice President Scientific and Regulatory Affairs, PDA

CC: Richard Johnson, PDA; Denyse Baker, PDA

Food and Drug Administration Draft Guidance
Glass Syringes for Delivering Drug and Biological Products: Technical Information To Supplement ISO Standard 11040-4
July 2, 2013

General comment: The risk to patient safety being addressed by this draft guidance document is specific to reported connectivity problems between prefilled needleless glass syringes and pin activated needle free connecting devices. PDA is not aware of a more general issue affecting connectivity between syringes conforming to ISO 11040-4 and standardized ISO 594-2 conical Luer Lock fittings. Therefore, PDA recommends that FDA limit the scope of this guidance document to the more specific topic of connectivity with pin activated needle free connecting devices but additionally does not put the main focus on modifying the syringe tip to fit the pin activated needle free connecting devices but also covers modifying the pin activated needle free connecting devices to fit the syringe

The following table of comments and proposed changes includes suggested wording to focus the guidance on this specific patient safety concern.

Line No.	Current Text	Proposed Change	Rationale
Page 3 Introduction	"Connecting devices" include needles, needless luer connectors, adapters and transfer units	"Connecting devices" include needles, **needleless** luer connectors, adapters and transfer units	Needless luer connectors is a typo that could be misread with unintended consequences.

Line No.	Current Text	Proposed Change	Rationale
Page 3 Introduction	The recommendations provided in this guidance document are applicable to the sponsor of an IDE, HDE, 510(k), or PMA for the following glass syringe products, and to the sponsor of an IND, BLA, NDA, or ANDA3 for a drug or biological product that is delivered with such a glass syringe product: 1. Needleless glass syringes prefilled…. 2. Empty glass syringes co-packaged… 3. Empty glass syringes intended for use…	The recommendations provided in this guidance document are applicable **1. To the sponsor of an IND, BLA, NDA, or ANDA3 for a drug or biological product that is delivered with such a glass syringe product: Needleless glass syringes prefilled….** **2. To the sponsor of an IDE, HDE, 510(k), or PMA for the following glass syringe products and to the sponsor of an IND, BLA, NDA, or ANDA3 for a drug or biological product that is delivered with such a glass syringe product: Empty needleless glass syringes co-packaged…** 3. **To the sponsor of an IDE, HDE, 510(k), or PMA for the following glass syringe products: Empty needleless glass syringes intended for use…**	To avoid misunderstanding in roles & responsibilities depending the type of product

Line No.	Current Text	Proposed Change	Rationale
Page 4 Introduction	1. Needleless glass syringes prefilled…. 2. Empty glass syringes co-packaged… 3. Empty glass syringes intended for use…	1. Needleless glass syringes prefilled…. 2. Empty **needleless** glass syringes co-packaged… 3. Empty **needleless** glass syringes intended for use…	All issues described are related to the needleless syringes Focus guidance on needleless syringes with ISO 594-1 and ISO 594-2 cone designs.
Page 4 Background	Typically, glass syringes…	Typically, **needleless** glass syringes…	All issues described are related to the needleless syringes

Line No.	Current Text	Proposed Change	Rationale
Page 5 III background	Because of these glass syringe connection events and associated adverse events, FDA has recognized that demonstrating conformity to the ISO 11040-4 standard alone does not ensure that the glass syringes can be properly connected to connecting devices. Therefore, sponsors who seek to rely on conformity to the ISO 11040-4 standard in submissions for glass syringe products should also submit information from supplemental tests to demonstrate that the glass syringe can be properly connected to connecting devices. The purpose of this guidance document is to identify the supplemental tests that should be performed, and to recommend possible design modifications, to ensure that glass syringes are properly connected to connecting devices.	Because of these glass syringe connection events and associated adverse events **with pin activated needle free connectors**, FDA has recognized that demonstrating conformity to the ISO 11040-4 standard alone does not ensure that the glass syringes can be properly connected **to pin activated needle free connecting** devices. Therefore, sponsors who seek to rely on conformity to the ISO 11040-4 standard in submissions for glass syringe products should also submit information from supplemental tests to demonstrate that the glass syringe can be properly connected to **pin activated needle free** connecting devices **or label that the devices are not to be used with these connections**. The purpose of this guidance document is to identify the supplemental tests that should be performed to ensure compatibility with **pin activated needle free connecting devices, and to** recommend possible **other alternatives** ~~design modifications~~, to ensure that glass syringes ~~are~~ **can** properly connect~~ed~~ to **pin activated needle free** connecting devices.	Focus guidance on needle free connectors, not glass syringes. The size orifice of the glass syringe can be important to the delivery of the therapeutic. All issues related to the incompatibility of glass needleless syringes are specific to the use with pin activated needle free connectors. These connectors, which are not subject to any standardization, have pins (whose dimensions are not standardized) which interact with the delivery orifice of the syringes. There are no safety advisories regarding the incompatibility of the syringes with the luer connectors for which they were designed to work.

Line No.	Current Text	Proposed Change	Rationale
IV. Question A	For example, the standard lacks dimensions for the glass syringe nozzle internal diameter, thickness of nozzle wall, and barrel neck curvature. In contrast, the standard for the connecting devices, ISO 594-2, has specified dimensions in these areas. Therefore, it is possible that a glass syringe that meets the ISO 11040-4 standard may not properly connect to a device that conforms to the ISO 594-2 standard. More specifically, conformance to ISO 11040-4 alone cannot ensure connectivity to connecting devices without breakage or other product performance failure as described above.	For example, the standard lacks dimensions for the glass syringe nozzle internal diameter **and**, thickness of nozzle wall. In contrast, the standard for the connecting devices, ISO 594-2, has specified dimensions in these areas. Therefore, it is possible that a glass syringe that meets the ISO 11040-4 standard may not properly connect to a **pin activated needle free connecting** device **and** conformance to ISO 11040-4 alone cannot ensure connectivity to **pin activated needle free** connecting devices without breakage or other product performance failure as described above.	These dimensions are not required to ensure compatibility with other ISO 594-2 standardized luer based connectors.

Line No.	Current Text	Proposed Change	Rationale
IV. Question B	**What other glass syringe dimensions are critical in addition to those specified in ISO 11040-4?** Generally, the dimensions for glass syringes that are not specified in ISO 11040-4 but that are important for the connection to connecting devices include the following: 1. Syringe inner and outer diameter, 2. Height of the nozzle for a glass barrel syringe intended to connect to a luer lock fitting, 3. Thickness of nozzle wall, 4. Barrel neck curvature, and 5. Dimensions to accommodate luer locks with a center pin piercing element.	**What other glass syringe dimensions are critical in addition to those specified in ISO 11040-4 for connecting to a pin activated needle free connecting device?** Generally, the dimensions for glass syringes that are not specified in ISO 11040-4 but that are important for the connection **to pin activated needle free** connecting devices include the following: 1. Thickness of nozzle wall, 2. Dimensions to accommodate luer locks with a center pin piercing element.	As shown in the Proposed Change, the two dimensions that should remain in the guidance are the syringe dimensions that could impact the connectivity of the syringe with pin activated needle free connecting devices, which is the stated problem and should be the focus of the guidance.

Line No.	Current Text	Proposed Change	Rationale
V	**V. WHAT IS FDA RECOMMENDING?** FDA recommends that sponsors submit data to demonstrate that their glass syringe has connectivity (interoperability) to connecting devices to ensure proper delivery of the drug or biological product. To achieve this, the glass syringe design and validation data should include information beyond the information needed to conform to ISO 11040-4. Recommended design or re-design options are listed in subsection A. The general types of data and information the Agency recommends in the premarket or investigational submission for glass syringes are listed in subsection B.	**V. WHAT IS FDA RECOMMENDING?** FDA recommends that sponsors submit data to demonstrate that their glass syringe has connectivity (interoperability) **to pin activated needle free** connecting devices to ensure proper delivery of the drug or biological product. To achieve this, the glass syringe design and validation data should include information beyond the information needed to conform to ISO 11040-4. Recommended-options are listed in subsection A.	Focus the guidance on the stated problem.
V. A. 1	A. What are the recommended design or re-design options? 1. Use bonded or staked needle with appropriate sharps protection feature for subcutaneous or intramuscular injections.	A. What are the recommended design or re-design options? 1. **If possible and/or compatible with the drug to be delivered and intended route of administration,** use a syringe **with a** bonded or staked needle	Sharps protection is not required and not relevant to this standard.

Line No.	Current Text	Proposed Change	Rationale
V. A. 2	2. Design the glass syringe with internal dimensions that ensure connectivity to connecting devices. (Although several designs may be possible, one example might be to enlarge the internal diameter of the glass syringe nozzle to accommodate pin-piercing design of needleless connectors.)	2. **If possible and/or compatible with the drug to be delivered and intended route of administration,** design the glass syringe with internal dimensions that ensure connectivity to **pin activated needle free** connecting devices. (Although several designs may be possible, one example might be to enlarge the internal diameter of the glass syringe nozzle to accommodate pin-piercing design of needleless connectors.)	Focus the guidance on the stated problem. By enlarging the inner diameter of the luer nozzle it automatically decreases the wall thickness of the luer. Consequences of such change on overall product performance must be assessed.
V. A. 3	3. Develop designs for dedicated dual connections between the glass syringe and connecting devices. For example, the designs may consist of a connecting device with dual connections: one end for the glass-syringe and one end for the connecting device with which it may be used. These dedicated connections may be appropriate for co-packaging with a prefilled syringe.	3. Develop designs for dedicated dual connections between the glass syringe and **pin activated needle free** connecting devices. For example, the designs may consist of a connecting device with dual connections: one end for the glass-syringe and one end for the connecting device with which it may be used. These dedicated connections may be appropriate for co-packaging with a prefilled syringe.	Focus the guidance on the stated problem.
V. A. 4	N/A	4. If compatibility with pin activated needle free connecting devices cannot be ensured, label the product to with WARNINGS that state the device is not intended for use with **pin activated needle free** connecting devices.	Focus the guidance on the stated problem and provide option to bridge to standardized needle free connectors.

Line No.	Current Text	Proposed Change	Rationale
V. B	**B. What data and information does the Agency recommend be included in premarket submissions?**	**B. What data and information does the Agency recommend be included in premarket submissions to demonstrate compatibility with pin activated needle free connecting devices?**	Focus the guidance on the stated problem.
V. B 1	1. Data and information demonstrating dimensional conformance to relevant FDA-recognized ISO standards to ensure compatibility with connecting devices: a. ISO 11040-4: applies to glass barrels of glass syringes b. ISO 594-2: applies to luer lock When a glass syringe is used with an injector or other device, additional ISO standards may apply. These are listed in the Section V.C of this document.	1. Data and information demonstrating conformance to relevant FDA-recognized ISO standards to ensure compatibility with **standardized luer based** connecting devices: a. ISO 11040-4: applies to glass barrels of glass syringes b. ISO 594-2: applies to luer lock When a glass syringe is used with an injector or other device, additional ISO standards may apply. These are listed in the Section V.C of this document.	Focus the guidance on the stated problem. Dimensional requirements of ISO 594-2 are not all applicable to glass syringe. Nevertheless, even if not exactly compliant with all dimensional requirements, glass syringes should comply with functional requirements. On-going revision of ISO 11040-4 and ISO 80369-7 (to replace ISO 594-2) will take that point into account.
V. B 2	For dimensional elements that are not addressed in the relevant ISO standards, but are otherwise critical for connectivity,…	For dimensional elements that are not addressed in the relevant ISO standards, but are otherwise critical for connectivity, **for example to pin activated needle free connecting devices**,	Focus the guidance on the stated problem.

Line No.	Current Text	Proposed Change	Rationale
V. B 3, V. B 4, V. B 5	3. Functional Performance of Syringe: The ISO standards include recommendations for the performance of glass syringes as stand-alone products, but do not include recommendations for the performance of these syringes when connected to connecting devices. Data to show syringe performance and proper connectivity in this context include, but are not limited to, the following:	3 Functional Performance of Syringe: The ISO standards include recommendations for the performance of glass syringes as stand-alone products, but do not include recommendations for the performance of these syringes when connected to **pin activated needle free** connecting devices. Data to show syringe performance and proper connectivity. **Demonstrate that it is fit for the intended use.** ~~a. Seal Integity~~ . . . p ~~Piston seal blowback~~ ~~4 Biocompatibility~~ ~~5 Sterilization~~	Focus the guidance on the stated problem. Tests regarding connectivity between glass syringe and pin activated needle free connecting should be performed only. V.B 3.a through 3.p, V.B 4 and V.B 5 are not unique to the stated problem and should be deleted from this guidance. FDA may wish to consider publishing separate draft guidance to address the general submission requirements for prefilled syringes, so that it can be reviewed and commented based on its appropriateness and value in the context of general submission requirements, not in the context of connectivity.
V.B 6	Analysis of use error is particularly important when products are re-designed to mitigate connectivity and compatibility issues such as those described in this document.	Analysis of use error is particularly important when products are re-designed to mitigate connectivity and compatibility issues **with pin activate needle free connecting devices such** as those described in this document.	Focus the guidance on the stated problem.

Line No.	Current Text	Proposed Change	Rationale
V. B 9	9. The submission to FDA describing each test performed should include a summary that explains the objective, acceptance criteria, sample size (statistically significant number with justification), method, results, discussion, and discussion of deviations.	9. The submission to FDA describing each test performed should include a summary that explains the objective, acceptance criteria, sample size (statistically significant number with justification), method**, executive summary of** results, discussion, and discussion of deviations. **Bracketing approach may be used when relevant.**	For prefilled syringes, in case the information is stated in DMF that covers several barrels design configurations, it may be not practically possible to add all design verification results in DMF. Raw data are available in design center site, for audit/inspection. Executive summary (e.g. mean, standard deviation) should be sufficient, and where justify, bracketing approach would enable to accelerate review.
V Closing paragraph	FDA notes that the above items focus specifically on the glass syringe connectivity aspects of development.	FDA notes that the above items focus specifically on the glass syringe connectivity aspects of development **related to pin activated needle free connecting devices.**	Focus the guidance on the stated problem.