Biotechnology Industry Organization

June 12th, 2014

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

Re: Docket No. FDA-2014-D-0248: Draft Guidance for Industry on Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products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Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the "Draft Guidance for Industry on Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products."

BIO represents more than 1,000 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.

GENERAL COMMENTS:

We commend the FDA on releasing this Draft Guidance, which we believe is consistent with industry practices for "fixed" dose regimens. In particular, we agree that single-dose vials should not contain a significant volume beyond what would be considered a maximum dose for the expected use of the drug product (lines 125-126). However, we note that there is little new information provided in the Draft Guidance; instead it points to already established documentation without much additional clarification. We believe it would be beneficial for Sponsors if the Draft Guidance added additional clarification and discussion around these topics.

In terms of the scope, the Draft Guidance discusses products that require reconstitution. However, BIO recommends exempting lyophilized products from the scope since lyophilized products are reconstituted by a healthcare provider — not the manufacturer — and manufacturers cannot be held accountable for an action over which they have no control beyond providing proper instructions for use. However, if FDA finds that lyophilized products are within the scope of this guidance, we suggest adding a separate

1201 Maryland Avenue SW
Suite 900
Washington DC 20024
202.962.9200
202.488.6306
bio.org

section of detailed guidance for lyophilized products, including acknowledgement that reconstitution should follow manufacturer provided instructions. Alternatively, FDA could establish a separate guidance for lyophilized products since the complexity of these products in terms of factors involved for determination of excess volume necessitates more clarity and harmonization across the industry.

We find that the term "allowable" as used in the title and text of the Draft Guidance is not clear as to whether it is referring to the expected overfill or maximum overfill. We ask the Agency to use either the term "maximum" if this is describing a specification limit or "expected" if this is describing a target volume.

While fixed dose regimes may account for the majority of drug and biological products administered, it is also important to note that there are exceptions and the Draft Guidance should retain an appropriate level of discretion and flexibility for these instances. For example, the Draft Guidance states in lines 128-129 that "consumers and/or health care providers should not be routinely required to use more than one vial to administer a typical single dose of the drug product." However, we note that this may not be efficient or effective, especially when the dosing paradigm is based on a body mass (mg/kg) or surface area (mg/m2) basis. BIO believes that there are instances where multiple sized-single-dose vials may be the appropriate option for a given patient. These may include:

- Primary vial(s) containing the dose requirement based on the average patient (*e.g.*, 20 mL x 5 mg/mL = 100 mg).
- Secondary vial(s) containing a lower amount of drug product that could be used to achieve the required dose (*e.g.*, 5 mL x 5 mg/mL = 25 mg dose adjustment).

Further, we believe that there are also cases for many biologics and some new molecular entities intended for direct injection (*e.g.,* without dilution) where a single vial paradigm is not technically feasible. These might involve drugs where the product has demonstrated stability concerns at higher concentrations, or tonicity concerns, pH concerns, *etc.*, that constrain the formulation development design space to lower concentrations.

Finally, we believe that a two-vial product format is currently gaining ground as an occasional industry practice in the biologics space and provides flexibility to the consumer and health care provider while avoiding excess waste and restraining the development cycle for novel product formats.

In light of these comments we believe that the scope of this guidance should be for single-dose vials only and not include multiple-vial, body mass, or surface area paradigms.

CONCLUSION:

BIO appreciates this opportunity to comment on the "Draft Guidance for Industry on Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products." Specific, detailed comments are included in the following chart. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

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

SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
Line 2:	The term "vial" is footnoted to mean vials and ampules. However, the discussion throughout the Draft Guidance is focused on single-dose (not variable dosing or weight based dosing) and liquid formulation.	We propose editing the footnoted definition of vial as follows: "The term *vial* used throughout this guidance refers to both single-dose liquid vial and ampule package types."
I. INTRODUCTION		
Lines 24-26:	The Draft Guidance discusses the importance of "appropriate packaging sizes" however the recommendations seem more focused on container sizes.	We propose editing the statement as follows: "This guidance also discusses the importance of appropriate ~~packaging sizes~~ container/vial volume for injectable drug products and recommends that labeled vial fill sizes be appropriate for the intended use and dosing of the drug product."
Lines 28-29:	The Draft Guidance discusses products that require reconstitution. However as discussed in our general comments above, we recommend exempting lyophilized products from the scope of the guidance. Additionally, the Draft Guidance does not discuss its applicability to variable dosing from single use vials. Although there are many examples of this type of dosing in the marking, including variable dosing from single-use vials would result in	We recommend that lyophilized product be outside the scope of this guidance and editing the statement as follows: "This guidance addresses fill and packaging issues for injectable drug products that are packaged in single-use/single-dose vials and ampules~~, including products that require reconstitution~~. This guidance does not apply to variable dosing from single-use vials." However, if FDA finds that lyophilized products are within the scope of this guidance we suggest adding a separate section of detailed guidance for lyophilized products,

SECTION	ISSUE	PROPOSED CHANGE
	potentially more presentations to address multiple dose options, increasing complexity.	including acknowledgement that reconstitution should follow manufacturer provided instructions. Alternatively, FDA could establish a separate guidance for lyophilized products since the complexity of these products in terms of factors involved for determination of excess volume necessitates more clarity and harmonization across the industry.
Lines 28-35:	The Draft Guidance does not clarify its applicability to legacy products.	We propose adding the following statement to the paragraph: This guidance does not immediately apply to legacy products unless there is a public health issue identified that is directly related to the specific dosage form.
Lines 32-35:	The Draft Guidance applies to NDAs, ANDAs, and BLAs; clarity is needed on whether this applies to variations for established products.	We request clarity on whether the Draft Guidance applies to variations for established products. If so, we recommend the statement to be edited as follows: "The recommendations in this guidance apply to new drug applications (NDAs), abbreviated new drug applications (ANDAs), biologics license applications (BLAs), as well as ~~new packaging supplements to these existing applications~~ changes to approved NDAs, ANDAs, and BLAs, submitted to CDER and CBER."
II. BACKGROUND		
Lines 45-48:	Examples of 'misuse' are vaguely addressed and fill volume is cited as a contributing factor. However, the Draft Guidance does not address that this	We suggest the Guidance include additional language clarifying "misuse" by consumers, and noting that this is a violation of current product labeling.

SECTION	ISSUE	PROPOSED CHANGE
	misuse is in fact a violation of existing product labeling. This is a recurring theme throughout the Draft Guidance. Also, in citing that misuse is being done by consumers and HCPs, there are no other solutions such as enlisting the aid of HCP practice associations or strengthening other product security features or labeling.	
III. OVERVIEW		
A. Allowable Excess Volume		
Lines 56-58:	The Draft Guidance uses the term "slightly exceeds the content indicated in the labeling" and references official USP drug product monographs. However, we believe the Draft Guidance could benefit from more clarity around this term.	We recommend that the guidance include more discussion on what is meant by "slightly exceeds" as referenced in line 57.
Footnote 6 (Lines 56-58):	Footnote 6 does not address variable dosing products.	The scope of the reference should be modified to refer only to single-use / fixed-dose presentations, or the footnote should be revised to describe only the maximum possible dose that could be administered.
Lines 58-59:	The Draft Guidance should be clarified to state that excess vial volumes are designed to allow for the full withdrawal and administration of the maximum labeled vial volume.	We suggest the statement be edited as follows: "The excess volumes are meant to be sufficient to permit withdrawal and administration of the maximum labeled volume."

SECTION	ISSUE	PROPOSED CHANGE
Lines 59-63:	The Draft Guidance discusses that the "declaration of net quantity of contents on the label is considered to express the minimum quantity of contents." We find the term "minimum quantity of contents" to be ambiguous.	We suggest the statement be edited as follows: "FDA regulations at 21 CFR 201.51(g) provide that for drugs in ampules or vials that are intended for injection, the declaration of net quantity of contents on the label is considered to express the minimum quantity of contents able to be delivered to the patient (*e.g.*, deliverable volume or nominal fill volume multiplied by minimal concentration of drug product) and further requires that variation above the stated measure must comply with the excess volumes set forth in USP."
Lines 63-66:	USP General Chapter <1151> Pharmaceutical Dosage Forms provides excess volume recommendations for mobile and viscous liquids in a range of container sizes, noting that the excess volumes recommended are usually sufficient to permit withdrawal and administration of the labeled volumes. The interpretation of USP<1151> table is quite different in the pharmaceutical industry on the following items: I. First Column (Labeled Size) of USP<1151> table: The labeled size can be interpreted as nominal fill volume or container size. This guidance refers to this column as "container size". Since only standard container sizes are available from glass manufacturers, there have been cases that different fill volumes may still	We request FDA provide more detailed clarifications on the mentioned items for USP<1151> Recommended Excess Volume Table.

SECTION	ISSUE	PROPOSED CHANGE
	use the same closest container size available (example: 1 mL and 2mL using 2mL container size). In addition, the syringe sizes for product withdrawal will vary based on fill volume. Considering the recommended excess volume should take into consideration both vial dead volume during product withdrawal and syringe dead volume during product injection, referring "Labeled size" as Nominal Fill Volume is more relevant for the purpose of recommended excess volume. II. In manufacturing of liquid vial drug products, in process control limits are set to ensure drug volume per container meets the Drug Product Specifications. It is unclear whether "Recommended Excess Volume" refers to minimum fill volume (Lower Control Limit), or Target Fill Volume in liquid vial drug products. In both cases, the volumes are higher than the nominal fill volume and can be interpreted as "Excess Volume".	
Lines 70-71:	The statement "FDA becomes concerned…" suggests a connotation that a subjective review of applications is being performed by FDA, as opposed to a science based review.	We suggest the first sentence be removed, and the statement be edited as follows: "~~FDA becomes concerned when the excess volume in a vial is greater or less than the USP recommended amount without appropriate justification.~~ Excess volume in greater or less than the USP recommended amount should be

SECTION	ISSUE	PROPOSED CHANGE
		justified in the submission."
B. Labeled Vial Fill Size		
Lines 78-79:	The Draft Guidance suggests that Sponsors identify appropriate fill volumes during product development based on how vials are likely to be used. This can be difficult if multiple doses are being evaluated in a Phase 3 program or if a Sponsor is attempting to bring forward multiple formulations (*i.e.,* SC and IV) of a single product. This is not always possible and does not address legacy products.	We suggest the Guidance include discussion and clarity on this topic.
Lines 79-82:	The guidance recommended "For example, single-dose vials are designed for use in a single patient as a single injection/infusion. However, even when appropriately labeled, single-dose vials that contain significantly more drug than is required for a single dose may result in the misuse of the leftover drug product". In cases that fill volumes less than 0.5 mL are required, in addition to vial and syringe dead volumes, limitations of drug product manufacturing such as vial size availability (2mL standard glass vials available for all fill volumes ≤ 2mL), filler capability, and other contributing factors may affect overfill. For very small fill volumes the ratio of overfill to intended fill	We suggest limiting this recommendation to fill volumes ≥0.5 mL.

SECTION	ISSUE	PROPOSED CHANGE
	is higher.	
Line 81 [footnote 8]:	The footnote on the term "significantly" is confusing. Since USP <1151> is able to specifically quantify reasonable excess volumes, it seems that is possible to specify a quantitative volume of remaining drug product that would generally be considered significant. This footnote does not consider USP <1151> which provides considerations on when an excess volume is significant and requires explanation to an individual reviewer.	We suggest referencing the injections overfill section of USP <1151> to address this topic.
Line 82:	Many products are currently approved where multiple vials may be combined to deliver a single dose and for which there is no larger vial available that would contain the single dose already. The guidance does not address this topic.	We suggest the Guidance include discussion on this topic.
Line 84-88:	This section discusses multiple-dose vials; however, the sole topic of this guidance should be single-dose vials as multi-dose recommendations of 30mL max is already included in USP <1>.	Please delete the discussion of multi-dose vials.
IV. DISCUSSION		

SECTION	ISSUE	PROPOSED CHANGE
Lines 92-93:	This section discusses following requirements in 21 CFR 201.51(g) and is interpreted as subcutaneous or intravenous. This guidance may not be appropriate for products that are diluted or infused via a medical device.	For clarity, we suggested editing the statement as follows: "With respect to allowable excess volume, the sponsor/applicant of drugs in ampules or vials, intended for direct injection, must follow the requirements in 21 CFR 201.51(g)."
Lines 92-95:	The CFR referenced establishes the label claim at the minimum, USP provides the target "excess volume" and 2 x USP provides the upper limit "allowable volume".	We request a more straightforward description of how these references can be applied for "expected" and "maximum" volumes.
Lines 107-108:	The Draft Guidance discusses sample collection during product development studies. However, in a clinical setting, pooling is unlikely (no reference to support this potential practice).	We suggest limiting the restrictions to products at commercialization.
Lines 110-111:	"Proposed excess volume" as used here seems to imply the target fill. We note that variable target may be needed for some products.	We suggest editing the text to read: "The applicant should provide data related to ~~proposed~~ maximum excess volume in the following sections of the application:"
Lines 110-118:	Volume studies are related to the suitability of the container closure system and data related to proposed excess volume should be located in P.2.4 Container Closure System.	Please edit the text to read: "The applicant should provide data related to proposed excess volume in ~~the following sections of the application:~~ 3.2.P.2.4 Container Closure. ~~• The excess volume included in a drug product should be described in the common technical document~~

SECTION	ISSUE	PROPOSED CHANGE
		~~(CTD) section 3.2.P.1, Description and Composition of the Drug Product.~~ • ~~The studies and justification (i.e., extractable volume testing, viscosity studies) should be described in CTD section 3.2.P.2.2.1, Formulation Development.~~
Lines 110-118:	In general, the extractable volume studies are performed using the representative material to justify the recommended excess volume. There are no guidelines for viscosity studies for justification of excess volume, variable among industry practice , and definition of viscous liquids in USP<1151> is unclear.	We ask FDA to provide more detailed explanation or examples on cases that viscosity studies are needed. We also ask for more clarity on how the Sponsor should justify the use of mobile liquids for recommended excess volume in USP <1151> table.
Lines 121-123:	Here and elsewhere within the Guidance, such as in the Introduction, it is suggested that justification can be provided by Sponsors for excess fill volumes. However, the Guidance does not provide examples describing what justifications may be appropriate.	We suggest the Guidance include examples of justifications that may be appropriate for Sponsors to provide for excess fill volumes (for example, orphan drug indications that are obtained post-marketing for a well-established product with a large history of use).
Lines 125-126:	It is unlikely to be an instance when a vial would be filled to what is considered a usual dose and that would not allow for the maximum dose.	We propose editing the statement as follows: "Single-dose vials should not contain a significant volume beyond ~~what would be considered a usual or~~ a maximum dose for the expected use of the drug product".
Lines 128-129:	The guidance recommended "Consumers and/or health care providers should not be	We suggest either removing this sentence or revise as follows:

SECTION	ISSUE	PROPOSED CHANGE
	routinely required to use more than one vial to administer a typical single dose of the drug product". As is mentioned above in our general comments, it is a common practice for biological drug products to use more than one vial (if needed) for doses that are administered based on weight (mg/kg) or surface area (mg/m2) dosing regimen. In addition, for biological drug products that are administered by IV infusion based on flat dosing regimen, there is a possibility of using more than one vial for preparation of IV bags.	Consumers and/or health care providers should not be routinely required to use more than one vial ~~to administer a typical single dose of the drug product~~ for a single dose of a drug product that is administered by direct injection based on flat dosing regimen.
Lines 131-132:	The footnote related to this statement [footnote 13] does not describe a specific circumstance.	We propose editing the statement as follows: "Multiple-dose vials should contain no more than 30 mL of drug product except under ~~specific~~ justified circumstances."
Lines 134-137:	The guidance recommends "The applicant should communicate with FDA early in the drug development process about the vial fill size and unique excess volume concerns. For example, applicants should consider such communications during the end of phase II meetings or other communications for investigational new drug applications (INDs)". For biological drug products in development, the dose is not finalized in Phase I/ II and therefore, there are possibilities of drug product configuration change (example: vial size,	We suggest revising as follows: For all application types, the applicant should communicate with FDA early in the drug development process about the vial fill size and unique excess volume concerns. For example, applicants should consider such communications during the end of phase II meetings or other communications for investigational new drug applications (INDs) or as soon as practicable after dosage and product configuration is established.

SECTION	ISSUE	PROPOSED CHANGE
	fill volume, excess volume) from phase I/II to phase III and commercial.	