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May 30, 2014

Ms. Leslie Kux
Assistant Commissioner for Policy
U.S. Food and Drug Administration
5630 Fishers Lane, Room 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Re: Docket No. FDA-2014-D-0248, Draft Guidance for Industry on Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products; Availability

Dear Ms. Kux:

The Association for Professionals in Infection Control and Epidemiology (APIC), HONOREFORM, and The Society for Healthcare Epidemiology of America (SHEA) thank the Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) for the opportunity to provide input into the draft guidance. Our organizations represent healthcare professionals, patients and consumers whose responsibilities include educating about and ensuring compliance with safe injection practices.

We are encouraged that the FDA is strengthening their industry guidance related to excess volumes and labeled fill sizes, as improper management and misuse of injectable medications and biologicals can result in microbial contamination and has been implicated in the transmission of bloodborne illnesses between patients. We share the FDA's concern about these inappropriate practices, as these outbreaks cause immeasurable harm to patients and result in significant cost in outbreak investigations, patient testing, treatment, and litigation.

As noted in the FDA guidance, USP General Chapter <1> allows for some overfill to provide sufficient amounts for the correct dosage of the medication or biologic to be safely withdrawn. However, excessive volumes in single dose/single use vials have on occasion contributed to bloodborne illness transmission because overfill volumes were pooled to obtain additional doses. Our organizations support limiting the amount of recommended overfill to the volumes prescribed in USP General Chapter <1>, as this will discourage pooling and sharing of single dose/single use vials.

More commonly, outbreaks have involved single dose/single use vials that were reused for multiple patients. This happens when the listed volume contains multiple doses for a particular application, which may be an "off-label" use, in which the medication is being used in a manner not specified in the FDA's approved packaging label, or insert. We encourage manufacturers to package products in appropriate vial sizes for dosages that reflect common uses. As an example, contrast agents are generally supplied in single dose vials, with the smallest vial being 10mL; however some users may only need 2-3mL at a time. This invites unsafe practices because there is no alternative for the user. Similarly, many other injectable medications are used "off-label" and involve doses smaller than the smallest single dose vial size available. The Draft Guidance states, "...sponsors should determine the appropriate

packaging sizes *during* product development, considering how the vials are *likely* to be used.” (Italics added for emphasis.) Logically, this principle should also apply *after* initial product development in consideration of *actual* use.

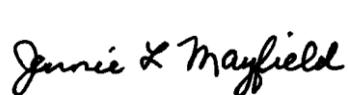
It would be very helpful to patients, providers, industry, and groups like ours if FDA exercised its influence to address this. We encourage the agency to provide guidance when it is aware that certain products are commonly used “off-label” to (1) remind facilities about safe injection practices, (2) identify acceptable alternatives (e.g., repackaging following USP standards or within the new category of 503B outsourcing facilities which follow Current Good Manufacturing Practices under FDA oversight), and (3) suggest that manufacturers consider selling product packages that are appropriately sized for that use. On this last point, FDA should consider whether its regulatory approval process imposes any unnecessary impediments. For example, we have been advised that generic injectable drug manufacturers may not propose smaller volume packaging than what was approved under the original manufacturer’s FDA application, without undergoing additional, potentially lengthy and cost-prohibitive reviews.

We also note that the FDA guidance document addresses the issue of multi-dose vials. The guidance notes that the maximum fill size for a multi-dose vial, according to USP General Chapter <1>, is 30mL. More specific guidance by the FDA may promote safer practices by the end user. We encourage the FDA to consider providing the guidance to allow for a smaller maximum fill size in multiples of a regular dose size (e.g., 3 times the usual dose), rather than the 30 mL maximum referenced above, or a maximum number of doses (e.g., for use in 3 doses). This might encourage manufacturers to size packages more realistically and encourage users to focus on safe use.

We appreciate the FDA’s efforts to improve patient safety and hope the agency will continue to address patient safety in future guidance to manufacturers in relation to vial fill size and excess volumes for weight-based dosing for parenteral medications and also in the context of drug shortages. Weight-based dosing introduces variability that challenges efforts to match vial size to dosages. The drug shortage issue is particularly vexing as manufacturers may produce large, medium and small size vials, but shortages of the drug may provide financial disincentives for the production and purchase of small “right-sized” vials by the manufacturer and users, respectively. Thus, the shortage issue overrides the safety issue.

Thank you for the opportunity to review this proposed rule and provide input on behalf of our members. We look forward to working with the FDA to continue to promote patient safety through improved manufacturing practices.

Sincerely,



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