FDA U.S. FOOD & DRUG ADMINISTRATION

April 16, 2018

Ms. Shawn Becker
Senior Director, Healthcare Quality Standards
The United States Pharmacopeial Convention, Inc.
12601 Twinbrook Parkway
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Dear Ms. Becker:

FDA is writing to reiterate our concerns about the United States Pharmacopoeia (USP)'s proposal in the draft <797> for the assignment of beyond-use-dates (BUDs) to compounded sterile preparations (CSPs) based on the dating in the applicable USP monograph, if such a monograph exists. FDA is similarly concerned about the proposal to assign BUDs based on a stability study. Stability studies are not sufficient to model the risk of microbiological contamination of a product each time it is produced, nor are they sufficient to predict the growth characteristics of any contaminating microorganisms. Assigning long BUDs that are not sufficiently supported by comprehensive, scientific microbiological data, and that are not reviewed by a regulatory agency with experience with such studies, could lead to significant microbial growth in a compounded sterile preparation (CSP) that has been contaminated. This could significantly exacerbate the harm caused by administration of a contaminated compounded drug.

Assigning a BUD based on an applicable monograph

For the following reasons, FDA recommends that the compounding USP monographs reference table 8 in the draft <797> for assigning the BUD. The BUD for a CSP should not exceed that which is specified in Table 8, and the BUD may be shorter if there are stability concerns that, as reflected in the monograph, necessitate a shorter date. This approach would recognize that a CSP with a monograph that demonstrates physical and chemical stability at a longer date is not any less prone to sterility assurance concerns than a different substance that is not the subject of a monograph.

FDA recognizes that USP develops the dating in monographs based on robust stability studies that demonstrate the physical and chemical stability of the substance through the BUD. FDA also recognizes that the studies demonstrate that the container is appropriate such that it does not leach into or otherwise react with the drug product. However, stability studies do not sufficiently model the risk of microbiological contamination during production. For example, USP monographs do not specify manufacturing sterilization details, such as autoclave time and

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temperature, and filter type and filtration pressure. Furthermore, the draft chapter <797> does not require the compounder to validate these sterilization processes, wear all sterile gowning items, or monitor environmental conditions during productions. For these reasons, the studies performed by USP to support each monograph do not represent the process or environmental conditions of every pharmacy that prepares the CSP.

In addition, including a policy in <797> that allows for longer BUDs based on a monograph will create an inconsistency in the chapter. For example, the same microbiological controls (e.g., cleaning/disinfecting, personnel qualification, environmental monitoring and media fill frequencies) and microbiological testing procedures (e.g., sterility and bacterial endotoxins) will be used at a given pharmacy to prepare its CSPs. Under the current proposal, two CSPs, one the subject of a monograph and the other not, could have widely different BUDs even though they were produced in accordance with the same conditions and processes.

During a recent teleconference, USP expressed concern that stakeholders have questioned a standard that requires assigning a drug product a default BUD even though the monograph provides for longer dating. USP similarly indicated that it would be difficult to articulate to stakeholders the rationale for the default BUDs more generally. We note that this concern would apply to any BUD for a CSP that is not the subject of an applicable monograph and for which a stability study has not been conducted. FDA would welcome collaboration with USP to discuss the rationale for the default BUDs.

Further, although FDA's primary concerns pertain to sterility issues, we also note that potency and container suitability may be a concern as well. The monographs do not always specify the type of container in which the drug product was tested, and use of a different container, perhaps of a different material, or use of different preparation procedures, could affect the stability of a drug product.

Stability studies

FDA is particularly concerned about the proposal to allow compounders to assign BUDs based on stability studies and recommends that USP remove the option for compounders to assign a BUD based on stability data. FDA is concerned that introducing stability studies as a mechanism to assign BUDs that exceed the default dating would create a substantial loophole for compounders to label their drug products with long BUDs without meaningful scientific justification.

First, we note that the proposed revision to chapter <797> does not provide guidance on what an adequate stability study would entail. In a recent teleconference, USP advised that it intends to consider developing, in a separate document, standards for stability studies. However, this would not address the interim period between the publication of chapter <797> and publication of standards for stability studies. During this interim period, FDA is concerned that compounders

will not have information about the testing that they would need to conduct to perform a meaningful stability study.

Further, it is FDA's understanding that a concern that prompted USP to initiate the process of revising chapter <797> was that the standards in the current chapter can be interpreted in a variety of ways and have, therefore, presented difficulties both for compounders that seek to comply with them and states that seek to enforce them. For the standards that USP is developing to have a meaningful public health impact, it is critical that they be specific enough for compounders and regulatory authorities to understand what is expected. A provision for stability studies, without any guidance on what that entails, would likely be difficult to interpret and enforce uniformly.

However, even if USP did provide detailed standards for conducting stability studies, concerns would remain. For example, FDA is concerned about the quality of the stability studies that compounders not subject to current good manufacturing practice requirements may conduct. To conduct a meaningful study that demonstrates that a drug product is sterile and stable through its BUD, an entity must conduct a number of tests that, in FDA's experience, state-licensed pharmacies, federal facilities, and physicians do not typically perform and are beyond their capabilities. When FDA has reviewed or become aware of stability studies conducted by compounding pharmacies, they have been deficient. For example, during a recent inspection, FDA noted that although a compounding pharmacy assigned a BUD to a drug product based on a stability study, FDA laboratory analysis of the drug product, which was within its BUD, revealed that it was 1% of its labeled potency.

Further, as USP is aware, FDA does not conduct inspections of the vast majority of compounding pharmacies in the United States. States have primary day-to-day oversight over such pharmacies and may not have the expertise to review stability studies, which are not typically required by states' laws. As noted above, long BUDs based on flawed stability studies could have significant public health implications.

Finally, FDA is concerned that the proposed chapter would allow compounders to rely on stability studies performed by another entity. Importantly, a stability study conducted by one entity may provide minimal insight on whether the drug product will remain stable when produced by a different entity. The materials (e.g., purity of the bulk drug substances, inactive ingredients, container) and processes at one pharmacy may differ from those of the entity that performed the study.

Sterility Testing

During a recent teleconference, USP suggested that performing a sterility test may mitigate FDA's concern with CSPs being labeled with BUDs that exceed the default BUDs in table 8. However, merely passing a sterility test does not indicate that a CSP batch is, in fact, sterile;

rather, adequate sterility assurance is a result of all activities that take place in a facility, including robust environmental and personnel monitoring.[1] We note that the newest revision of the chapter has significantly decreased monitoring activities as compared to the initial draft chapter that appeared in the PF. Since not all these sterility assurance activities are accounted for in the monographs or in the newest revision of the chapter, BUDs unsupported by microbiological contamination risk data should be set conservatively, as reflected in table 8. The table 8 BUDs reflect a compromise that balance the quality risks associated with CSPs and the need for patient access to CSPs. Longer BUDs would require scientific support currently not required under the new revision to the chapter.

Conclusion

As USP is aware, once a drug intended to be sterile is contaminated and the longer it is held before administration, the greater the potential for microbial proliferation. FDA has investigated numerous outbreaks associated with patients who received contaminated compounded drug products labeled with a long BUD.

FDA's concerns associated with the proposals to assign BUDs based on the dating in the monograph or a stability study are rooted in our experience responding to outbreaks associated with compounded drugs. Pharmacies, federal facilities, and physicians that compound sterile drug products look to USP standards to understand the practices and conditions that must be met to produce a sterile and otherwise high quality product. Many states similarly look to USP standards for inspections and enforcement. The revisions pertaining to BUDs would send a concerning signal to these entities that assigning a BUD based on monograph dating that is divorced from sterility assurance, or based on any stability study that they conduct no matter its content or rigor, is acceptable. This would constitute a significant loosening of the standards that USP initially proposed to raise the bar for sterile compounding broadly and decrease the potential for serious patient harm associated with contaminated compounded drug products.

FDA appreciates your attention to this important matter and looks forward to continuing to work with USP by providing scientific input on the development of standards pertaining to drug compounding.

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[1] From *USP* <71> *Sterility Tests* – "These Pharmacopeial procedures are not by themselves designed to ensure that a batch of product is sterile or has been sterilized. This is accomplished primarily by validation of the sterilization process or of the aseptic processing procedures…A(a) satisfactory result only indicates that no contaminating microorganism has been found in the sample examined under the conditions of the test."

Sincerely,

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