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Alliance for Pharmacy Compounding

May 6, 2021

Connie Sullivan
Chairman, USP Compounding Expert Committee <797> Subcommittee
U.S. Pharmacopeia
126 Twinbrook Parkway
Rockville, Maryland 20852

RE: USP <797> Beyond-Use Date Recommendations

Dear Chairman Sullivan:

On behalf of the Alliance for Pharmacy Compounding, and as chair of APC's Beyond-Use Date Task Force, I wish to offer input that we believe can assist your subcommittee's work to determine proper beyond-use date standards for sterile compounded preparations.

As you may know, the Alliance for Pharmacy Compounding (formerly the International Academy of Compounding Pharmacists) is the voice for pharmacy compounding, representing thousands of pharmacists, technicians, students, researchers and suppliers. Compounding exists for patients and animals who are not served by traditional pharmaceutical manufacturers. We create custom medications that patients simply cannot get anywhere else. Every day, our members play a critical, often life-or-death role in patients' lives. Pharmacy compounders are a valued part of the health care team, creating essential treatments unavailable elsewhere for a range of issues, including autism, oncology, dermatology, ophthalmology, pediatrics, women's health, and many others.

APC and its members have a great interest, of course, in the updated USP <797> chapter that was published in June of 2019. Along with other stakeholders, we appealed the new <795> and <797> chapters developed by USP based on our grave concerns about the restrictions on beyond-use dates in those chapters, and we understand that the current work of your subcommittee is the result of the granting of our appeal in March of last year.

On behalf of APC's Beyond-Use Date Task Force, I wish to share our recommendations regarding default BUDs for sterile products in Chapter <797>.

As a baseline matter, APC firmly believes that default BUDs for sterile compounded preparations need to be based on scientific evidence. We understand the need for default dates that apply to the greatest number of compounds in order to establish a consistent regulatory enforcement regime. However, as highly trained scientists, pharmacists should be able to avail themselves of many different resources to apply appropriate BUDs to compounded sterile products (CSPs). Preventing us from extending BUDs

with testing will result in greatly reduced access to CSPs by our patients, increased cost to those patients, and will induce pharmacies to create smaller, more frequent batches of CSPs that are not tested for sterility at all.

The main source of confusion for us regarding the default BUDs published in the 2019 USP Chapter <797> is this: Were these default BUDs based on the achievement and maintenance of sterility for CSPs (sterility assurance) or were they based on the chemical and physical stability of CSPs (stability)? We assume both sterility assurance and stability were factors in establishing these default BUDs for CSPs, and our recommendations below are based on that assumption. However, it remains unclear to us what specific sterility assurance practice standards published in the 2019 USP Chapter <797> were of greatest concern to USP and contributed to the establishment of the short default BUDs. For example, currently there are 22 compounded sterile preparation monographs that USP has published with BUDs of up to 180 days. But these monographs contain no additional sterility assurance requirements beyond those specified in <797>. This leads us to believe that USP's main concerns regarding extended BUDs for CSPS are based more on a compounder's ability to demonstrate chemical and physical stability of a CSP over time, including container-closure integrity and antimicrobial effectiveness, and less on whether a compounder can achieve sterility during the compounding process by following the standards already established in Chapter <797>.

We propose that USP create a Category 3 that would allow pharmacies compounding batches with extended BUDs (Category 3) to perform stability indicating studies and/or have greater QA/QC requirements than pharmacies that use the default BUDs. In the following pages, we provide suggestions as to what could be added to the requirements in USP <797> to allow pharmacies to extend BUDs, including proposed cleaning requirements and greater frequency of environmental and personnel monitoring. The increased requirements would be more rigorous than <797> procedures, but less rigorous than cGMP requirements.

RECOMMENDATIONS

Category Definitions

We recommend no changes to the proposed Categories 1 and 2, but we urge the creation of a new Category 3 that provides for extending the BUD of a CSP to at least 180 days and up to one year, under the storage conditions studied. Beyond the proposed <797> guidelines, this would require:

- Limited stability-indicating BUD studies be performed to establish true chemical/physical/ microbiological stability for a specific compound
- A QA/QC program that meets at least minimum standards, as proposed below, to ensure higher quality aseptic processes to warrant longer BUD dates
- That USP-compliant sterility and endotoxin testing be performed on each lot produced if extended BUDs beyond USP <797> defaults are to be assigned.

Limited Stability-Indicating BUD Study Requirements

One of the challenges to pharmacies wishing to perform stability indicating studies is understanding exactly what is required. We suggest that USP develop guidance along these lines, providing pharmacies with a clear definition of such studies. A good start might be a USP chapter on stability studies for 503a pharmacies that is numbered above <1000> for informational guidance, but not necessarily referenced in USP <797> as an enforceable chapter. This would provide best-practice industry guidance while allowing the flexibility of testing needed for a very wide array of CSPs.

Some suggestions for the content of such a chapter include:

- A requirement that stability-indicating studies must develop a stability-indicating assay that attempts forced degradation to differentiate between peaks related to the analyte versus peaks related to excipients, degradation products, impurities, or other matrix components. Additionally, having USP clearly define how to attempt forced degradation would be very helpful to industry and would improve the quality of these drug products for patients. Some information to clarify might include, for example, relevant stress conditions used in forced degradation (such as heat, humidity, light, oxidation, acid, and/or base). Additional clarification on processes to follow for formulations that are unable to undergo forced degradation would also be beneficial.
- Appropriate laboratory tests to be performed at various time points after a stability-indicating assay is developed. For example, at which time points in a BUD study should we minimally test potency, pH, sterility per USP <71>, endotoxin per UPS <85>, container closure, particulate matter, and antimicrobial effectiveness per USP <51>?
- Definitions and descriptions of appropriate bracketing, matrixing, and accelerated BUD studies. This would provide clarity to 503A pharmacies and various regulators on best practices, and of course give critical guidance to pharmacies.
- If a USP monograph, or a published or unpublished stability study for a CSP exists, the compounding pharmacist should be able to use the BUD established by that study if:
    - the additional QA/QC procedures proposed below are followed.
    - the formula is followed exactly.
    - a container closure study is performed.
    - sterility and endotoxin testing is performed on every batch.

Other Recommendation Notes

In order to extend BUDs, we recommend several additional QA/QC procedures in addition to those in the proposed chapter <797> revision, most notably increased frequency of environmental monitoring. The ability to ensure the suitability of a sterile compounding environment is arguably one of the most important factors in the ability to produce a sterile final product.

Cleaning/Personnel Competency/Process Verification

We recommend using only sterile disinfectants/sporicides and sterile IPA in the primary engineering control and other ISO 5 areas. We also recommend increasing the frequency of gloved fingertip sampling of compounding personnel to at least every two weeks.

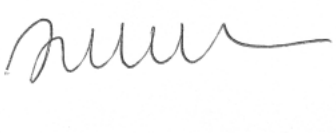
Environmental Monitoring

We also propose increasing surface sampling to at least every two weeks in all ISO 5 areas, and monthly in other controlled air environments. We recommend increasing the frequency of viable air sampling to at least monthly. Identification of organisms recovered would be required if growth exceeds action limits, as is proposed in the current proposed <797> revision. We propose no changes to the nonviable air sampling regimen found in the current proposed <797> revision.

That concludes our recommendations.

We truly appreciate USP's and your subcommittee's openness to receiving input from all stakeholders regarding the updates to the chapters, specifically related to the proposed default BUDs. Thank you for this opportunity to share our recommendations.

Sincerely,



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C: APC Board of Directors
APC Beyond-Use Date Task Force