Date: August 16, 2019

To: Derek L. Shaffer, Partner, Quinn Emanuel Urquhart & Sullivan, LLP ("Quinn Emanuel")

Cc: Barry Siegel, General Counsel, Wedgewood Village Pharmacy, LLC
Shawn E. Hodges, President, CEO, Innovation Compounding, Inc.
Scott Brunner, Executive Vice President, International Academy of Compounding Pharmacists ("IACP")

From: Mario Sindaco, Vice President, Science—Operations and Executive Secretariat, Council of Experts, USP

Regarding: Appeal of Revisions of Beyond-Use Date Standards in General Chapters <795> and <797>

Dear Mr. Shaffer:

This correspondence sets forth the Compounding Expert Committee's decision and rationale in response to Quinn Emanuel's appeal, submitted pursuant to Article VII, Section 7 of the Bylaws of the United States Pharmacopeial Convention ("USP"), and Section 7.08 of the Rules and Procedures of the 2015-2020 Council of Experts ("CoE Rules"), on July 31, 2019.

Under Article VII, Section 7 of USP's Bylaws, the Expert Committee establishing the standard or standards being appealed shall work with a sense of urgency to reconsider the standard(s) and issue a decision. In light of the significant work that the Compounding Expert Committee has undertaken to date in the revision of General Chapters <795> and <797> – including their review of a combined total of more than 6,400 public comments on these standards – the Committee was prepared to evaluate the materials Quinn Emanuel provided expeditiously. Their decision and rationale are summarized in the following pages.

Quinn Emanuel's appeal requested that USP withdraw the proposed revisions related to beyond-use dates ("BUDs") in <795> and <797> or delay any change to the BUD portions of the chapters so as to provide additional time to work with stakeholders.[1]

USP acknowledges Quinn Emanuel's submission, along with references to T.A. du Plessis, *The Shelf Life of Sterile Medical Devices*, 13 S. AFR. ORTHOPAEDIC J. 32, 33–34 (2014) (hereinafter "Exhibit A") and Frances W. Bowman, *The Sterility Testing of Pharmaceuticals*, 58 J. PHARMACEUTICAL SCI. 1301 (1969) (hereinafter "Exhibit B").

Upon careful consideration, the Compounding Expert Committee ("CMP EC" or the "EC") has decided to:[2]

[1] We recognize that your submission included points related to USP's standards-setting authority and process. The appeals provisions set forth in USP's Bylaws contemplate challenges to standards adopted by the Council of Experts. This response is limited in scope to addressing your scientific and substantive challenges to the standards themselves.

1) Maintain the requirement for stability-indicating assays for extending BUDs for compounded nonsterile preparations ("CNSPs") in <795>.
2) Maintain the BUD framework for CNSPs in General Chapter <795>.
3) Maintain the BUD provisions for compounded sterile preparations ("CSPs") in General Chapter <797> with the commitment to develop resources for extending BUDs to include stability, sterility, and monitoring (personnel and environmental) considerations.

The rationale for these decisions is explained further below.

1) Maintain the requirement for stability-indicating assays for extending BUDs for CNSPs in <795>.

During the public comment period for the proposed revision of General Chapter <795>, USP received comments related to the requirement for stability-indicating assays for extending BUDs for CNSPs. A stability-indicating method is required for extending BUDs for CNSPs because of its ability to quantitate the active ingredient and its degradation products or related impurities in the preparation by separating the active ingredient from its degradation products and impurities, and its ability to show a change in the concentration of the active ingredient with increasing storage time.

In contrast, a potency (or strength) study only determines the amount of active ingredient in a preparation. Depending on the analytical method used in a potency study, it may not be able to separate the active ingredient from its degradation products and impurities for quantitation. Interference from drug-related impurities or degradants could be hidden within the peak area measured or not detected at all by the particular method conditions.[3]

Similarly, commenters have noted that a photodiode array ("PDA") detector coupled with high-performance liquid chromatography ("HPLC") has the capability to provide accurate results free from interference. However, one of the limitations of such an approach is that the ultraviolet ("UV") scan is not necessarily specific and small changes in the drug molecule can occur that may not be detected by the scan but may alter the drug strength, even though based on the assay, the strength may not have changed. The molecule may contain chromophores that absorb the UV light at different wavelengths and efficiencies. If a molecule degrades but the change is not in a strong chromophore, then the change will not appear in the scan, and the strength will not be determined accurately.

Although modern HPLC detectors can evaluate peak purity, peak purity evaluation should be performed on every analysis to confirm that nothing is hidden, assuming the impurity/degradant is detected by the detector employed (e.g., PDA or mass spectrometer). Even if peak purity is performed, some changes in degradation levels can still be missed,

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[2] In accordance with USP's rules and policies regarding conflicts of interest, all members of the CMP EC were invited to discuss the appeal. However, members with conflicts of interest related to the General Chapters under appeal recused themselves prior to final discussion and voting.

[3] *See* Loyd Allen Jr, Gus S Bassani, Edmund J Elder Jr, and Alan F Parr, *Strength And Stability Testing For Compounded Preparations*, U.S. PHARMACOPEIAL CONVENTION (Jan. 13, 2014), https://www.usp.org/sites/default/files/usp/document/FAQs/strength-stability-testing-compounded-preparations.pdf.

especially when a very low level of degradant or impurity forms in a highly concentrated sample whereby the potency may not be affected by this change, but the amount of impurity could still be enough to exceed toxicologically acceptable levels. Peak purity is often used to supplement or support development of a stability-indicating assay, but should not be relied upon in place of proper method development and validation.

A properly validated method, based on General Chapter <1225> *Validation of Compendial Procedures*, should pre-determine that separation of impurities and degradants has been established. The method should not be based on checking for interference and then adjusting as needed. In addition, not every degradation product will have chromophores and be detected by UV analysis; thus, evaluation beyond the UV spectrum may be warranted. General Chapter <1225> also requires validation that goes well beyond just peak purity determination, including accuracy, precision, specificity, limits of detection/quantitation, linearity, range, and ruggedness.

The revised <795> permits BUDs for aqueous and nonaqueous dosage forms to be extended up to a maximum of 180 days if there is a stability study using a stability-indicating assay for the active pharmaceutical ingredient ("API"), CNSP, and type of container-closure that will be used. The stability study may be published or unpublished for the particular formulation of interest. Bracketing studies, where the stability study is performed on a low concentration and a high concentration of the active ingredient while maintaining the same concentrations of other ingredients, may also be performed to determine stability across a range of strengths. The container-closure system is important because of the potential for container-drug interaction where substances may have either sorptive or leaching properties. For example, if stability is determined for a particular CNSP formulation stored in amber plastic bottles, compounders should use an amber plastic bottle for dispensing.

The intent of the provision for stability-indicating assays in General Chapter <795> is to ensure the stability of the formulation, minimize the risk of degradants and impurities that may have toxicological effects, and minimize the risk of microbial proliferation. In the absence of such stability testing, *Table 3* in the revised <795> provides a conservative approach to assigning BUDs based on the stability and microbial considerations. The BUDs in the table continue to ensure patient access to needed formulations while minimizing the risk of decomposition, incompatibility, and microbial proliferation.

Furthermore, the revised General Chapter <795> allows assigning of BUDs for CNSPs for which there is a *USP-NF* compounded preparation monograph. USP has developed numerous compounded preparation monographs based on stability studies supported by stability-indicating assays for medications that have a high public health need, that are essential to treat pediatric and geriatric patients, that are needed to avoid allergic reactions, and for unmet clinical and therapeutic needs. USP continues to develop compounded preparation monographs and would welcome stakeholder input on formulations for monograph development.[4]

[4] U.S. PHARMACOPEIA, *Compounded Preparations Monographs (CPMs)*, *available at* https://www.usp.org/compounding/compounded-preparation-monographs.

2) Maintain the BUD framework for CNSPs in General Chapter <795>

In the revised <795>, the framework for assigning BUDs for CNSPs was changed in response to public input and to address the need to consider microbial susceptibility of certain CNSP formulations. The previously published chapter characterized preparations as "nonaqueous" or "water-containing." These characterizations were eliminated to clarify whether a substance containing waters of hydration or vehicles containing a small portion of water are considered "water-containing." The concept of water activity was added in the revised chapter to assess the susceptibility of a nonsterile preparation to microbial contamination and the potential for degradation due to hydrolysis. Water activity is further described in General Chapter <1112> *Application of Water Activity Determination to Nonsterile Pharmaceutical Products*. CNSPs prepared in a nonsterile environment from nonsterile ingredients will have some level of microbes which may proliferate over prolonged storage especially if the formulation does not contain any preservatives. Further, formulations with a higher water activity may support microbial growth. Solid dosage forms are expected to have low water activity and thus have the longer BUD of 180 days.[5] Since General Chapter <795> does not require microbial testing of formulations, the BUDs in *Table 3* for CNSPs are intended to mitigate the risk of excessive microbial contamination.[6]

The BUDs in *Table 3* are assigned based on the consideration of stability, compatibility, and microbial proliferation in the CNSP. In the revised framework, nonaqueous dosage forms (e.g., suppositories, ointments, fixed oils, or waxes) will have a default BUD of 90 days and solid dosage forms will have a default BUD of 180 days. In comparison to the currently official chapter, nonaqueous formulations have a default BUD of 180 days. From a stability perspective, the CMP EC remains concerned that not all nonaqueous formulations other than solid dosage forms are stable for 180 days. Many compounders assume that fixed oil formulations are inert and not active, however, oils may be reactive to certain substances. Studies performed in oil formulations in the course of developing USP compounded preparation monographs[7] have shown API decomposition before 180 days. The CMP EC additionally noted that compounders may inappropriately formulate CNSPs in oil formulations in order to use the longer BUDs even though such formulations may not be clinically appropriate (e.g., risk of aspiration).

The CMP EC determined that BUDs should not be extended more than 180 days based on stability testing. General Chapter <795> recommends, but does not require, antimicrobial effectiveness testing if BUDs for CNSPs are extended beyond those in *Table 3.* While stability results may show that the formulation is stable for 180 days, it does not ensure that the CNSP does not contain excessive microbial contamination. Further, the CMP EC felt that there was not a clinical justification to require extension of BUDs beyond 180 days. Patients often return for their refill before 180 days and most third-party payers do not reimburse for a 6-month supply of medication.

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[5] *See also* General Chapter <1112> *Application of Water Activity Determination To Nonsterile Pharmaceutical Products,* 42 U.S. PHARMACOPEIA – NAT'L FORMULARY 7688 (Nov. 1, 2018) (stating that "nonaqueous liquids or dry solid dosage forms will not support spore germination or microbial growth due to their low water activity.")

[6] *See also* General Chapter <61> *Microbiological Examination Of Nonsterile Products: Microbial Enumeration Tests*, 42 U.S. PHARMACOPEIA – NAT'L FORMULARY 6387 (Nov. 1, 2018).

[7] *Supra* note 4.

Finally, the CMP EC determined that the BUD provisions in <795> are not severable from the chapter. The approach to BUDs is an integral component of General Chapter <795>, which cannot be delayed separately from the rest of the chapter.

3) **Maintain the BUD provisions for CSPs in General Chapter <797> with the commitment to develop resources for extending BUDs to include stability, sterility, and monitoring (personnel and environmental) considerations.**

The BUDs in the revised General Chapter <797> are assigned based on a risk-based approach. The BUDs in *Table 11* for Category 2 CSPs are based on several factors including aseptic processing and sterilization method, starting components, sterility testing, and storage conditions. The BUDs balance the frequency of personnel monitoring (e.g., gloved fingertip sampling and media-fill testing every 6 months) and environmental monitoring (e.g., total particle count and viable airborne monitoring every 6 months; and surface sampling monthly) with the need to facilitate patient access and to ensure patient care in the event of shipment delays.

During the public comment period for General Chapter <797>, numerous commenters requested the ability to extend BUDs for CSPs. The revised chapter does not provide provisions for extending BUDs because of the need for additional testing such as for stability, sterility, endotoxin, container-closure integrity, and particulate matter, as well as personnel and environmental monitoring which are specific to each facility. Such provisions are needed to ensure the stability and sterility of the formulation. Evidence from outbreak events has shown that contaminated vials stored for longer periods of time allow for microbial proliferation and increased risk of harm to patients.[8] The maximum BUDs in *Table 11* for Category 2 CSPs are intended to mitigate the risk of inadvertent contamination or the risk of not sterilizing the CSP.

Reliance on literature sources and direct testing alone does not ensure that the CSPs are sterile. While a stability study can be performed using a stability-indicating assay, compounders must also consider sterility of the formulation. Stability studies do not ensure that a batch is sterile (as noted in Exhibit A) and the frequency of environmental and personnel monitoring in the revised General Chapter <797> may not provide adequate sterility assurance for CSPs with extended BUDs. Further, sterility testing performed by one facility for a particular formulation cannot be extrapolated to the same formulation prepared by another facility. The facilities may have different personnel, different facility design and engineering controls, and different procedures in place. The personnel and environmental monitoring results would be specific to their respective individual facilities.

Sterility testing provides a point in time result of a formulation and provides some level of assurance of sterility but is not by itself "designed to ensure that a batch of product is sterile or has been sterilized."[9] As noted in Exhibit A, the CMP EC agrees that sterility testing alone does not demonstrate that an entire batch is sterile. For extending BUDs, the CMP EC determined that other considerations must be in place such as more frequent personnel and environmental monitoring. Further, acknowledging that sterility testing is changing rapidly, as

[8] Marion Kainer, et al. *Fungal Infections Associated with Contaminated Methylprednisolone in Tennessee*, 367 NEW ENG J. MED. 2195 (Dec. 6, 2012).
[9] *See* General Chapter <71> *Sterility Tests*, 42 U.S. PHARMACOPEIA – NAT'L FORMULARY 6407 (Nov. 1, 2018).

noted in Exhibit B, General Chapter <71> has evolved and has been revised since 1969. Additionally, General Chapter <797> expressly permits validated alternative sterility testing methods.[10] The sterility assurance levels ("SALs") described in Exhibit A for medical devices may be different from those CSPs. The revised General Chapter <797> describes probability of a nonsterile unit ("PNSU") of 10^{-6} (also called SAL) for terminal sterilization methods. Container-closure integrity (or packaging integrity as noted in Exhibit A) is also an important consideration for extending BUDs. For extending BUDs beyond those in *Table 11*, compounders must consider other key parameters to ensure both stability and sterility.

Finally, the CMP EC determined that the BUD provisions in <797> are not severable from the chapter. The framework of <797> is based on Category 1 and Category 2 CSPs which are distinguished primarily based on the environment in which they are prepared and their BUDs. The BUD provisions cannot be delayed separately from the rest of the chapter.

The decision of the CMP EC summarized above reflects years of deliberation and stakeholder engagement in the form of public comment review, roundtables, workshops, open face-to-face meetings, and open microphone sessions. There have been several published reports highlighting the importance of quality standards for compounded sterile drugs to minimize the risk of harm to patients.[11] Based on the evidence presented to the CMP EC to date, it is the Committee's view that the revised versions of General Chapters <795> and <797> appropriately minimizes the risk of patient harm in the areas of nonsterile and sterile compounding, respectively.

The decision of the CMP EC summarized above does not foreclose the possibility of future revisions to these chapters. Standards in the *USP-NF* are in continuous revision, and the EC is committed to further engagement with stakeholders to develop additional resources including those for extending BUDs.

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This letter reflects the CMP EC's decision and rationale in response to Quinn Emanuel's appeal. Should you have any questions about the above, please direct them to Mario Sindaco, Executive Secretariat (mys@usp.org or (301) 816-8246).

[10] *See also* General Chapter <1222> *Validation of Alternative Microbiological Methods*, 42 U.S. PHARMACOPEIA – NAT'L FORMULARY 9508 (June 3, 2019).
[11] Janet Woodcock & Julie Dohm, *Toward Better-Quality Compounded Drugs — An Update from the FDA*, 377 NEW ENG. J MED 2509 (Dec 27, 2017). Nadine Shehab, Megan Brown, Alexander Kallen & Joseph Perz, *U.S. Compounding Pharmacy-Related Outbreaks, 2001–2013: Public Health and Patient Safety Lessons Learned*, 14 J. PATIENT SAFETY 164 (Sept. 2018). Charles E. Myers, *History of sterile compounding in U.S. hospitals: Learning from the tragic lessons of the past*, 70 AM. J. HEALTH-SYSTEM PHARMACY 1414 (Aug. 15, 2013).