BRIEFING: CONCERNS ABOUT NEW USP <795> AND <797> CHAPTERS' TREATMENT OF BUD DATES

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The United States Pharmacopeia Convention ("USPC") has proposed significant revisions to USP General Chapter <797> Pharmaceutical Compounding—Sterile Preparations ("USP <797>") and to USP General Chapter <795> Pharmaceutical Compounding—Nonsterile Preparations ("USP <795>"). The proposed revisions are scheduled to become effective on December 1, 2019. Among other things, those revisions would shorten the beyond-use dates ("BUDs") assigned to compounded sterile preparations ("CSPs") and to compounded nonsterile preparations ("CNSPs").

We believe the proposed revisions lack scientific basis and will severely and negatively impact patient safety and care. The following outlines our concerns.

Not only do the proposed standards lack scientific support, but they ostensibly ignore accumulated scientific evidence and insightful comments submitted by numerous parties, who specifically pointed out defects and problems with USPC's proposed revisions. Unless USPC changes course, as it should, the revised USP chapters will inadvertently harm patients by, among other things, disrupting their medical treatment and continuity of care and preventing continuing use of therapies that are now standards of practice in medicine, without any medical justification. Moreover, USPC's rationale for the shortened BUDs is based on the unsupported premise that the existing USP <797> standards cannot provide adequate assurance of sterility, thereby calling into question the value of the entire chapter. In addition, the shortened BUDs will have a profoundly negative impact on patient safety due to lack of availability and/or treatment interruptions.

By revising USP <797> so as to incorporate substantially shortened BUDs with no allowance to extend BUDs, USPC has ignored overwhelming scientific evidence and consensus that commend no such change. USPC has decided unilaterally and inexplicably that compounders are unlikely to achieve or maintain sterility when preparing CSPs in accordance with USP <797> unless they also perform unnecessary and expensive sterility testing. Relatedly, USPC has arrived at impractically short BUDs based largely on sterility testing, thereby departing dramatically from established practice without any discernible, much less commensurate, justification.

If USPC has concerns that the compounding standards set forth in USP <797> are inadequate for ensuring the sterility of compounded medications, the appropriate course of action would be to promulgate heightened compounding standards under USP <797>, not to arbitrarily shorten BUDs. Under revised USP <797>, all CSPs, regardless of the conditions under which they are prepared, are presumed to have a high risk of non-sterility, resulting in drastic shortening of BUDs. The BUDs specified in the revised USP <797> inexplicably and unfairly discount the more rigorous practice standards required throughout the rest of USP <797>—practice standards that appropriately require compounders to implement additional processes and controls that together ensure a very high likelihood of maintaining and achieving sterility.

In drastically shortening BUDs, USPC places unwarranted emphasis upon sterility testing. As USPC and all informed observers well understand, sterility is maintained or achieved by utilizing well-controlled processes that are scientifically proven, as then simply confirmed by batch-level sterility testing. Unfortunately, the instant revisions ignore these fundamental principles in limiting CSPs to cripplingly short BUDs that have been arbitrarily established and no longer correspond with scientific indicators of sterility assurance. In sum, scientific consensus calls into serious question whether the absence of sterility testing alone warrants any (let alone drastic) shortening of the BUD for a particular CSP; conversely, the BUD for a CSP should not be extended beyond what science supports merely because the CSP has been subject to a sterility test.

As an example of how the BUD revisions are patently illogical when viewed in light of other provisions of USP <797>, as well as the prior standards, consider a CSP prepared from only sterile starting components and processed aseptically. Under existing USP <797>, in the absence of sterility testing, this CSP could be assigned a maximum BUD of 48 hours when stored at room temperature, 14 days refrigerated, or 45 days frozen. Under the revised USP <797>, this same CSP would now be assigned a maximum BUD of four days when stored at room temperature, 10 days refrigerated, or 45 days frozen.

This new BUD assignment indicates that USPC has concluded that this CSP suddenly poses a ***lower*** sterility risk when stored at room temperature (thereby warranting a longer BUD); a ***higher*** sterility risk when refrigerated

(thereby warranting a shorter BUD), and an ***equal*** sterility risk when frozen, as compared to the risks it posed previously. But nothing supports those conclusions, which defy credulity on their face.

At their core, the revised <797> BUD assignments rest on a false assumption. In particular, USPC is effectively telling the entire compounding industry that sterility testing alone plays a greater role in reducing sterility risk than ***the actual sterilization processes and methods used to prepare the CSP***. For instance, an aseptically processed CSP, stored at room temperature, that passes sterility testing, would now, under the revised USP <797>, be permitted a maximum BUD of 30 days. A terminally sterilized CSP, also stored at room temperature, that does not undergo sterility testing would be permitted a maximum BUD of 14 days:

STORED AT ROOM TEMPERATURE	**ASEPTICALLY PROCESSED**	**TERMINALLY STERILIZED**
Sterility Testing Performed	30 days	45 days
Sterility Testing Not Performed	1 - 4 days	14 days

The revised USP <797> therefore reflects the assumption that a terminally sterilized CSP that did not undergo sterility testing poses a ***higher*** risk of microbial contamination than an aseptically prepared CSP that passed sterility testing. This is inconsistent with credible scientific research.

Additionally, because the time it takes to conduct a sterility test counts against a CSP's BUD, the usable life of sterility-tested CSPs' will be clipped even more drastically than revised USP <797> contemplates. Sterility testing a CSP batch will likely take up to 20 days. As a result, the practical impact of the theoretic BUDs outlined in the revised USP <797> on the usable life of most CSPs, when sterility tested, would be:

STORED AT ROOM TEMPERATURE	**THEORETIC BUD**	**USABLE LIFE**
Aseptically Processed	30 days	10 days
Terminally Sterilized	45 days	25 days

Not only would a 10- to 25-day usable life require patients to obtain multiple fills of CSPs to complete even short-term medication therapy, these impractically short shelf lives would make it next to impossible for compounders to ensure they have adequate amounts of these CSPs available for immediate dispensing, thereby causing delays and interruptions to patients' treatment. Because non-sterility tested CSPs would be more readily available, the revisions to USP <797> may actually have the unintended effect of *disincentivizing* sterility testing.

Many other examples exist that demonstrate that the revisions to USP <795> and USP <797> are ill-conceived and should not be implemented. The proposed revisions are neither based on scientific evidence nor sensible by their own terms. Moreover, the revisions will disrupt the sound, established therapeutic regimens of patients and practitioners alike, and will strike a damaging blow against healthcare providers' ability to effectively treat patients.

We strongly encourage USP to heed the concerns of a growing coalition of concerned compounding pharmacies, prescribers, patients, and boards of pharmacy, and revisit the BUD restrictions in your revisions to USP <795> and USP <798>.

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