



January 20, 2020

Dear Appeals Panel,

My name is Dr. Loyd Allen, and I am writing on behalf of the Coalition in my capacity as an expert on compounded sterile preparations (CSPs) and compounded nonsterile preparations (CNSPs) to express my concern that the United States Pharmacopeia's (USP) revisions to General Chapters <795> and <797> are fundamentally misguided and scientifically unsupported. In particular, and as discussed further below, I am primarily concerned that the revised standards—especially those governing beyond-use-dates (BUDs)—are onerous, cost-prohibitive, and not supported by sound science. Ultimately, I fear that these revised standards will have significant, detrimental impacts on patients across the country, and specifically those in rural areas that lack access to alternative sources of compounded pharmaceuticals. More specifically, what is primarily lacking in both General Chapters <795> and <797> are considerations for the levels of risk associated with compounding for a small number of patients versus a large number of patients. The risk levels are totally different and should be addressed as such. The revised Chapters fail to do so. It doesn't matter if a patient comes from a rural or an urban community—their needs are important and it is our duty as healthcare professionals to meet those needs as appropriate.

I am also troubled that the process USP employed to arrive at the revised Chapters appears to have been improperly shielded from public view and driven by external, private interests. I was honored to serve USP for 40 years, but the Food and Drug Administration's (FDA) involvement in the standards setting process threatens USP's core values of independence and objectivity. In short, the FDA has continually and increasingly exerted its influence on USP to the point where, at least in the compounding arena, it appears to be highly influential—if not in control—of what occurs at USP. As a result, I am sharing my concerns as you determine whether USP should reconsider these influential standards.

Before giving my substantive comments, however, I'd like to tell you about my background as it relates to pharmaceutical compounding.

### **My Background and Experience**

My entire professional career has been devoted to teaching, practicing and supporting compounding pharmaceuticals. I earned a B.S. and M.S. in Pharmacy from the University of Oklahoma in 1966 and 1970, respectively. In 1972, I earned a Ph.D. in Pharmacy from the University of Texas. I have been a registered pharmacist in the state of Oklahoma since 1966. I have taught pharmacy at the university and professional level since 1970, including at the

University of Oklahoma Health Sciences Center and the P\*Ceutics Institute in Houston, Texas. Before entering academia, I was a practicing pharmacist in Massachusetts, Arizona, and Oklahoma.

Since 1990, I have been the CEO of the Midwest Institute of Research and Technology, which is a pharmaceutical consulting and contract research organization serving both the pharmaceutical and pharmaceutical compounding industries. I also serve as the Editor-in-Chief of two prominent pharmaceutical/pharmaceutical compounding publications: the International Journal of Pharmaceutical Compounding (since 1996) and Remington: The Science and Practice of Pharmacy (since 2011). I also author *The Art, Science and Technology of Pharmaceutical Compounding*, now in its fifth edition.

I was involved with USP's work from 1973-2013. In those 40 years, I served on numerous USP Expert Committees, Advisory Panels, and other committees. I was a member of USP's original Pharmacy Compounding Advisory Panel from 1990 to 2000, which essentially defined a role for USP in pharmacy compounding. I also participated in the meetings between USP and FDA that ultimately resulted in the development of General Chapters <795> and <797>, and later served on USP's Expert Committee on Nonsterile Pharmacy Compounding from 2000-2005 (Chair); 2005-2010 (Chair); and 2010-2013 (member). As Chair/member of the Expert Committee on Nonsterile Pharmacy Compounding, I was intimately involved in all aspects of the committee's work, including writing and revising General Chapter <795>; developing monographs for compounded preparations (including outsourcing laboratory testing, etc.); and considering and developing new chapters related to pharmacy compounding.<sup>1</sup>

I am proud to have served USP in numerous capacities for 40 years. But the recent revisions to Chapters <795> and <797> are troubling for a number of reasons, and in light of their potential impact on patients, I am compelled to share them with you.

### **USP's Standards-Setting Process and FDA's Influence on It**

In my view, the Food and Drug Administration (FDA) has an inappropriate level of influence on USP's General Chapter revision process that basically renders USP obsolete. But that was not always the case. In fact, for most of my tenure with USP, there was minimal involvement by the FDA. They did have a representative at meetings and, occasionally, more than one. FDA was generally a "resource" and provided input when it was requested. However, over the years, the involvement of FDA increased significantly to the point it had numerous representatives who routinely interjected their opinions, even though they were not requested. Some of the FDA representatives were quite good, but some were not and some did not even seem to know their own material as completely as one would expect for establishing enforceable, science-based standards.

In the last few years, it seems as if FDA participation has continued to increase to the point that their input is basically "running the show," which makes one wonder why USP continues to exist

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<sup>1</sup> For more information on my background and experience, please see my C.V., which I have attached to this letter as Exhibit A.

as a separate entity (one strongly influenced by the FDA). Frankly, if FDA gets what it wants, there is no need for USP to be involved in developing Professional Practice Standards.

This was never the intended state of affairs. General Chapters <795> and <797> resulted from a meeting back in the 1990s or early 2000 we (USP Staff, Dr. David Newton and myself) had with FDA where FDA expressed its concerns with compounding. Coming out of that meeting, there was general agreement that if USP prepared chapters related to standards in pharmacy compounding, FDA would be generally satisfied and refrain from further intrusion into compounding. Obviously, FDA did not live up to its part of the bargain and has continued to intrude into the affairs of USP related to compounding.

In the case of the revisions to General Chapter <797>, it appears that FDA's intrusions continued all the way up until the Chapter's final revisions. In that regard, I would point the Appeals Panel to the letter from FDA to Shawn Becker dated April 16, 2018. It is very illuminating and documents the efforts of FDA to control the standards developed by the USP Pharmacy Compounding Expert Committee. It is of interest that the 5-page letter discusses BUDs, but there are a lot of "coulds" and other wording that is not substantive but simply projects what "might" happen, and the discussion is without any documentation of adverse effects related to the current use of BUDs and the need for further changes.

To me, it is totally inappropriate for FDA to have sent this letter and for both USP and FDA to maintain its secrecy for so long. The process used here lacks transparency and scientific honesty. This is not how USP's revision system should work if openness and frank discussion of science-based standards for compounding is the goal. It is truly unfortunate that FDA provided USP a document that essentially served as a template or standard for what FDA wanted to accomplish in the revisions of Chapter <797>. USP is designed to be independent and science-based—not dependent and FDA-based.

Additionally, there seems to be a lack of acceptance of reasonable comments from external stakeholders during the public comment periods for Chapters <797> and <795>. USP received about 1,400 comments from interested practicing pharmacists concerning its proposed revisions to Chapter <797>. Of these, only about 1/3 were accepted and 2/3 were denied.

### **USP's Handling of Conflicts of Interest**

I also wish to share some concerns about the way USP handles conflicts of interest, including during the recent revisions to Chapters <795> and <797>. In my view, a key issue is that USP's current system of recruiting Expert Committee members invites those from conflicted areas to participate in the USP activities—to the point of even helping to develop and vote on substantive material. These conflicted individuals should only be on Expert Panels for discussion and should not be in decision-making or decision-influencing roles.

I saw these issues play out with respect to some of the revisions to Chapters <795> and <797>, which appeared to fall under the specific interests or auspices of some committee and panel members involved as consultants, providers of equipment, etc. For example, Eric Kastango, who chaired the Chapter <797> subcommittee while I was finishing my tenure on the Chapter <795>

committee, has a consulting firm that is directly involved in working with pharmacies to meet the standards of General Chapters <795>, <797> and <800> (and still does). He was probably the mover and shaker for Chapter <797> content revisions. In his professional position, Mr. Kastango does a good job, but his participation in USP business is a definite conflict of interest.

In addition, the most recent revisions to Chapters <795> and <797> appear to follow a growing trend of developing standards more complex than necessary and which require consultants, facility modifications, and new equipment that may be associated with the business/consulting interests of some members of the Expert Committee or Advisory Panels. Obviously, if one is involved in the type of business related to USP compliance for compounding, they should definitely not be involved in writing and approving the Chapters. Unfortunately, it seems that some of these individuals are far too influential in the Expert Committee's work, and this needs to be changed.

### **The Scientific Deficiencies of Revised Chapters <795> and <797> and Their Impact on Pharmacists and Patients**

I want to begin by saying that a revision of a General Chapter should only be undertaken when absolutely justified and should be supported by scientific justification, as changes in any specification can be costly, time-consuming, and sometimes onerous. Regarding compounding-related content, changes can even result in decreasing the availability of pharmaceuticals to patients when compounding pharmacies opt out of compounding due to overly ambitious and arbitrary standards, especially those that are not scientifically supported or justified—as is the case with the revised Chapters <795> and <797>.

My view of the revised Chapters <795> and <797> is that they are generally not scientifically supported by any evidence, but rather by “opinions” and what some individuals think “should be done.” It seems that in many cases the new requirements for compounding activities are similar or the same as the requirements for manufacturing facilities. Thus, there is only a threshold level of compliance and not a graduated hierarchy to allow lower-risk facilities some leeway to serve their patients safely and effectively. The risk factors are different but are not addressed or utilized in the standards. There is, evidently, no scientific data showing that the previous Chapters <795> and <797> were problematic and required revisions—only opinions.

As just mentioned, the issue of greatest concern regarding the revised compounding chapters is their failure to account for the differences in small- versus large-scale compounding. In the past, these chapters have been fairly reasonable and achievable with the goal of enhancing the quality of compounded preparations. Indeed, the original and earlier revisions of <795> and <797> were widely accepted. However, the revised standards have become much more onerous, cost-prohibitive, and appear to be patterned after industry standards where tens of thousands of dosage units are made. Indeed, many of USP's responses to the Coalition's appeal are only appropriate for manufacturing and not for the compounding of one or two patient-specific preparations (in everyday compounding, it may be that only one unit or several units are produced at a time). The exorbitant costs to implement the new USP standards (Chapters <795>, <797>, and <800>) has caused some pharmacies to discontinue compounding, and others are awaiting the outcomes of these appeals to determine what they are going to do. The bottom-line

issue is the lack of availability of compounded medications to tens or hundreds of thousands of patients daily when the standards become so strict that it is no longer feasible for a pharmacy to expend the resources necessary for compliance. This is a major issue in areas outside of the larger metropolitan areas where other compounding pharmacies may exist as alternatives for patients. In the Midwest, West and other areas, these alternatives often do not exist. Frankly, it appears that FDA and USP have little or no concern for the availability of individualized medications for the population outside of the larger cities. Some of these patients will be left without their medications, which can impact their health, quality of life, and even life itself.

In particular, a serious problem is that there are no graduated levels for nonsterile or sterile compounding based upon the number of preparations compounded daily. In other words, there is no relationship between the USP standards and the level of compounding activity a pharmacy does. For example, if a compounding pharmacy does one (1) compounded prescription per day—whether sterile or nonsterile or hazardous, etc.—it is required to be completely compliant with the Chapters the same as if they do five hundred compounded prescriptions a day, whether sterile or nonsterile or hazardous, etc. This does not seem rational, as the risk levels are considerably different for the pharmacies and personnel involved. Differences such as these are accounted for in some other USP General Chapters, which only require compliance for certain categories of action. Not so in the compounding chapters.

USP's apparent indifference towards patients in rural areas may stem from FDA's dim view of the ability of small compounders to conduct quality stability studies. This issue surfaced in FDA's April 16, 2018 letter to USP:

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.

This statement is incorrect and misleading, as many of the laboratories involved in performing stability studies in pharmaceutical compounding also do identical work for the FDA, USP, pharmaceutical companies, and Section 503b outsourcing facilities. The involved laboratories are also FDA registered and FDA inspected, so the quality of their work is on par with any laboratory used by cGMP facilities. It is therefore confusing why FDA would doubt the ability of these compounders to perform/contract for adequate stability studies. Overall, FDA's condescending statement simply illustrates a lack of knowledge concerning how stability studies are conducted; continues to promote nonscientific verbiage; and exhibits FDA's lack of current, valid documentation to make such statements.

It also appears in FDA's letter that there is no situation where FDA is in favor of compounded sterile preparations with extended BUDs. But FDA offers no documentation suggesting a problem exists with pharmacies that are compliant with the pre-revision standards.

Finally, I would like to briefly address the portion of USP’s response to the Coalition’s appeal that attempts to justify USP’s decision to maintain the BUD framework for CNSPs in General Chapter <795>. USP’s discussion regarding the use of General Chapter <1112> and water activity is something of a red herring and not really applicable. USP’s serial use of the word “may” is not definitive nor does it demonstrate that there is a documented issue with the way the nonsterile preparations have been characterized in the current Chapter. Far more definitive is the fact that the reduction in maximum BUDs is significant and problematic from both the pharmacist’s and the patient’s standpoint. Also, even though an active pharmaceutical ingredient (API) may have some water of hydration within its chemical structure and no growth occurs in the powder, when that API is placed in a nonaqueous matrix, neither USP or FDA cite any documented report of problems (microbial growth) that would merit a reduction in the BUD from 180 days to 90 days. And even if that situation did occur, an antimicrobial preservative could be added for microbial growth prevention. In establishing BUDs, physical and chemical stability are of the utmost concern, and Chapter <1112> simply does not address that issue. Furthermore, Chapter <1112> does not distinguish between “bound” and “unbound” or “free” water.

What is more, the use of Aw (water activity) to define dosage forms and categorize their “chemical stability” is not applicable, as Aw was never described for this purpose in USP <1112>. According to USP <1112>:

The determination of the water activity of nonsterile pharmaceutical dosage forms aids in the decisions relating to the following:

- (a) optimizing product formulations to improve antimicrobial effectiveness of preservative systems,
- (b) *reducing the degradation of active pharmaceutical ingredients within product formulations susceptible to chemical hydrolysis,*
- (c) reducing the susceptibility of formulations (especially liquids, ointments, lotions, and creams) to microbial contamination, and
- (d) providing a tool for the rational for reducing the frequency of microbial limit testing and screening for objectionable microorganisms for product release and stability testing using methods contained in the general test chapter *Microbial Enumeration Tests <61>* and *Tests for Specified Microorganisms <62>*.

Throughout USP <1112>, the discussion relates ONLY to (a), (c) and (d) above and there is NO further mention of (b). The sole purpose of USP <1112> involves microbial growth and testing related to Aw; it has nothing to do with chemical drug degradation. It provides no scientific basis for establishing chemical and physical beyond-use dates.

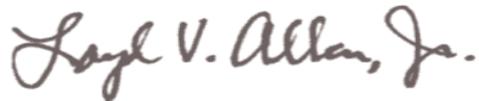
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As I have explained, my concern is that the revised standards outlined in Chapters <795> and <797> are unduly onerous, cost-prohibitive, and not supported by sound or documented science. . Moreover, the process USP utilized to arrive at the revised standards appears to have been improperly influenced by FDA. As a result, I am sharing my concerns as an expert witness on behalf of the Coalition. I support of the Coalition's request that the proposed revisions to Chapters <795> and <797> be vacated and that a newly formed Compounding Expert Committee reevaluate, with the benefit of new public comments, the issue of whether, and to what extent, any revisions to the Chapters <795> and <797> are necessary.

Sincerely,

A handwritten signature in cursive script that reads "Loyd V. Allen, Jr." The signature is written in dark ink and is positioned below the word "Sincerely,".

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Loyd V. Allen, Jr., Ph.D., R.Ph.