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July 31, 2019

Compounding Expert Committee
United States Pharmacopeia
12601 Twinbrook Parkway
Rockville, MD 20852-1790

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

Dear Compounding Expert Committee:

I write respectfully to appeal on behalf of a coalition of compounding pharmacies and professional associations ("Coalition") pursuant to Article VII, Section 7 of the Bylaws of the United States Pharmacopeia Convention ("USPC"). Specifically, the undersigned Coalition is hereby appealing USPC's proposed revisions to USP General Chapter <797> Pharmaceutical Compounding—Sterile Preparations and to USP General Chapter <795> Pharmaceutical Compounding—Nonsterile Preparations (collectively, "the Chapters"). Among other things, those revisions would shorten the beyond-use dates ("BUDs") assigned to compounded sterile preparations ("CSPs") and to compounded nonsterile preparations ("CNSPs"), which, in turn, will severely and negatively impact patient safety and care. As a result, the Coalition is appealing these changes and requesting that USPC withdraw the proposed revisions relating to BUDs or, at a bare minimum, delay any changes to the BUD portion of the Chapters so as to provide additional time to work with stakeholders to ensure patient access and safety. At the same time, the Coalition stands ready, willing, and able to assist the Expert Committee in arriving at appropriate BUD dates along with other protocols that both protect the interests of the public and ensure patient access to needed medications.

The Coalition is comprised of a respected, important group of industry stakeholders: the International Academy of Compounding Pharmacists, Innovation Compounding, and Wedgewood Village Pharmacy. These Coalition members, either directly or through their member organizations, are deeply involved with the development or dissemination of CSPs or CNSPs, and they are concerned that their patients and/or other constituents will be severely and adversely affected by USPC's worrisome and ill-considered revisions to the Chapters.

As elaborated below, the restrictive BUD standards are substantively indefensible: They pose a grave threat to established pharmacy and medical practice, and, ultimately, to the care and well-being of patients. Not only do the proposed standards lack scientific support, but they ostensibly ignore (or, at best, inexplicably discount) accumulated scientific evidence and insightful comments submitted by various Coalition members, who specifically pointed out defects and problems with USPC's proposed revisions. Unless USPC changes course, as it should, the revised 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. Whereas no science suggests that the new standards will improve patient safety, there are overwhelming indications that the new standards will have precisely the opposite of their intended effect. Below, the Coalition draws attention to the relevant body of evidence and associated concerns that should lead USPC to reconsider its proposed changes. We sincerely hope that USPC will now meaningfully grapple with and account for the substantive concerns we set forth herein, which, in our view, USPC has yet to do.

In raising our substantive concerns, we are also obliged to note our distinct but related concerns about the process by which USPC arrived at its revisions. Simply stated, we believe USPC's composition and process to be illegal for present purposes, as explained herein. Because the Coalition is focused on proper compounding standards and patient safety, its stated procedural concerns are very much secondary to its substantive concerns. We are appealing because USPC has, from our perspective, gone so badly astray with its changes to the Chapters. In noting how USPC's revisions would upend the compounding industry, medical practice, and patient treatment, however, we consider it appropriate and necessary to note that USPC has proposed its revisions in violation of law. While we appreciate this opportunity for appeal and welcome USPC's careful consideration, therefore, we must also advise you that all rights are reserved, and that at least one Coalition member contemplates pursuing appropriate legal recourse should that prove necessary.

It appears that USPC is effectively serving as a proxy for the Food and Drug Administration ("FDA") and regulating on FDA's behalf, while circumventing the Administrative Procedure Act ("APA"), 5 U.S.C. § 551 *et seq.*, and requirements of notice-and-comment rulemaking that constrain FDA. That, in and of itself, is improper. To the extent USPC considers itself a private party that functions outside of the federal government and constraints on same, it should not be operating as a *de facto* extension of FDA and equating FDA's inputs and say-so with scientific evidence or imperatives. Alternatively, to the extent USPC is operating hand-in-glove with FDA, it should be no less constrained by administrative law and due process than FDA is. By no account should USPC be effectuating what amount to seismic changes in the rules governing the compounding industry, without providing any reasoned justification for doing so or otherwise complying with the most basic and essential requirements of the APA. Yet that is what USPC has done in arriving at its vague and scientifically unsupported revisions to the Chapters.

The Coalition further questions the constitutionality of USPC's peculiar status under federal law. The guidelines propounded by USPC are especially concerning because they are slated to assume force of law under the Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. § 301 *et seq*. But the FDCA has effectuated, in our view, an unlawful delegation of law-making authority

to a non-governmental entity—and, in particular, to a *private organization*. The U.S. Court of Appeals for the D.C. Circuit had held such a delegation of lawmaking authority to a private entity to be *per se* unconstitutional. *See Ass'n of Am. Railroads v. U.S. Dep't of Transp.*, 721 F.3d 666, 668 (D.C. Cir. 2013), *vacated on other grounds and remanded sub nom. Dep't of Transp. v. Ass'n of Am. Railroads*, 135 S. Ct. 1225 (2015). In addition, courts insist that any delegation by Congress, even to the Executive Branch, be constrained by an "intelligible principle." Yet no such intelligible principle is in place to constrain USPC. Although FDCA's delegation to USPC has not yet been specifically tested in the courts, the available precedent renders the constitutionality of that delegation dubious, at least by our reading.

Even if Congress's delegation of law-making authority to USPC were constitutionally permissible (and we believe it is not), the process and procedures by which USPC arrived at the revisions to the Chapters fail to satisfy the minimum procedural protections demanded by the Due Process Clause of the Fifth Amendment to the U.S. Constitution combined with the APA. For one, USPC has offered scant insight into why it changed the BUD standards or what, if any, scientific evidence it purports to rely on. What is more, USPC has dismissed serious, penetrating comments opposing its proposed revisions without offering satisfying explanation or justification. Nor do the threadbare procedures announced in USPC's Bylaws and the Rules and Procedures of the Council of Experts afford adequate substitute for the procedures and protections the APA affords in order to safeguard due process. We candidly do not know, for instance, the process, standards, and rules by which USPC will now be considering and deciding this appeal. It is anomalous and disquieting to see USPC pulling the rug out from under compounders, physicians, veterinarians, and patients while shrouding its process and rationale in opacity. USPC should not be regulating like FDA without affording due process and transparency like FDA. As such, all rights are reserved to the extent that the upshot of the appeal leaves the Coalition or any member substantively aggrieved.

For these reasons, as elaborated below, the Coalition respectfully urges USPC to reconsider the revisions to the Chapters and to reengage relevant stakeholders in a full, fair, and transparent, engagement in order to arrive at sensible and scientifically supported standards for beyond-use dates, which it has not done thus far.

BACKGROUND

USPC is a private organization that develops a wide-ranging set of quality standards governing the production of pharmaceuticals. USPC's nationwide quality standards were first published in the nineteenth century and have become authoritative. In fact, for well over a century, USP standards have been incorporated by reference into both federal and state pharmaceutical law. As of today, USPC plays a key role in the regulation of the pharmaceutical industry, has immense power to alter the scope and substance of federal law, and sets standards that carry force of law and must be complied with by participants across the pharmaceutical industry.

USPC publishes an annual pharmacopeia called the United States Pharmacopeia ("USP"), which consists of a set of standards for medicines, food ingredients, dietary supplement products, and ingredients. These standards are used by regulatory agencies, manufacturers, and health care

practitioners to help ensure that these products are of the appropriate identity, as well as strength, quality, purity, and consistency. The Coalition's appeal is focused on General Chapters <797> and <795> of the USP, which establish standards for the preparation of sterile and non-sterile compounds, respectively. Among other things, the Chapters assign BUDs to CSPs and CNSPs, which, generally speaking, refer to the time beyond which a compound can no longer be used. Recently, USPC's Compounding Expert Committee decided—for reasons that are not entirely clear but appear to have been driven by FDA—to revise the Chapters, including as to the way in which BUDs for CSPs and CNSPs are calculated. Thus, the Committee released proposed revisions to the Chapters, contemplating significantly shortened BUDs for both CSPs and CNSPs. Prior to adopting its proposed revisions, the Committee also solicited comments from the public.

Coalition members submitted comments to the Committee. For example, the International Academy of Compounding Pharmacists and Wedgewood Village Pharmacy offered three primary reasons for why the shortened BUDs for CSPs were problematic. First, they explained that the BUDs were not based on science, conflicted with scientifically sound information found elsewhere in USPC's standards, and as such could harm USPC's credibility. Second, they explained that the rationale for the BUDs was based on the premise that the Chapter <797> standards could not provide adequate assurance of sterility, thereby calling into question the value of the entire chapter. And third, they explained that the short BUDs would have a profoundly negative impact on patient safety due to lack of availability and/or treatment interruptions.

On June 1, 2019, USPC published the revised Chapters in the USP. If formally adopted as proposed, the Chapters will become effective on December 1, 2019. Notably, USPC's revisions to the Chapters did not incorporate or acknowledge the Coalition's concerns about the impact of shortening the BUDs for CSPs and CNSPs, including the specific concerns identified by the International Academy of Compounding Pharmacists and Wedgewood Village Pharmacy identified above. Instead, the revisions maintained arbitrary, illogical, and disruptive rules for assigning BUDs. For example, Chapter <797> previously assigned BUDs based on two factors: a CSP's nonsterility risk factor and its storage conditions. But now, under the revision, BUD assignment is based on five factors: (i) whether a CSP falls into "Category 1" or "Category 2"; (ii) whether it was aseptically processed or terminally sterilized; (iii) whether it was sterility tested; (iv) whether it was prepared from sterile or nonsterile starting component; and (v) its storage conditions. *See* USP GENERAL CHAPTER <797> PHARMACEUTICAL COMPOUNDING—STERILE PREPARATIONS ("CHAPTER <797>") § 14. Thus, under this new system, all CSPs, regardless of the conditions under which they are prepared, are presumed to have a high risk of nonsterility, and will therefore have drastically shorter BUDs; that, in turn, will lead compounders to make smaller batch sizes and increase costs. In this respect, the Coalition determined that an estimated 91% of the CSPs they or their member organizations compound will be assigned shorter BUDs under the new regime—with the average BUD for CSPs being shortened by up to five months. As explained more below, the shortened BUDs are scientifically unsupported and will be detrimental to patient care.

Much the same is true for UPSC's revisions to Chapter <795>, which likewise create a new BUD assignment system. Previously, Chapter <795> assigned BUDs based on whether a CNSP was a water-containing oral formulation, a water containing topical/dermal formulation or

a mucosal liquid and semisolid, or a nonaqueous formulation. The revision divides CNSPs into four categories for BUD purposes: (i) non-preserved aqueous; (ii) preserved aqueous; (iii) nonaqueous; and (iv) solid. *See* USP GENERAL CHAPTER <795> PHARMACEUTICAL COMPOUNDING—NONSTERILE PREPARATIONS ("CHAPTER <795>") § 10. Again, these new standards have been derived without scientific justification and will drastically shorten the maximum BUD for solid CNSPs at the ultimate expense of patients.

Accordingly, the Coalition respectfully objects to these changes on both substantive and procedural grounds. *First*, the revisions to the Chapters are neither based on scientific evidence nor sensible by their own terms. *Second*, the revisions will disrupt the sound, established therapeutic regimens of patients and practitioners alike, and will strike a damaging blow against the compounding industry along with all those who depend on it. *Third*, the changes are invalid and vulnerable to legal challenge because USPC's incorporation into federal law entails an unconstitutional delegation of legislative powers by Congress to a private entity. *Finally*, even if USPC's role in federal regulation of the pharmaceutical industry were otherwise permissible, USPC has failed to satisfy the requirements of due process, as any state actor and/or agent of a federal agency would need to do when adopting new standards or regulations. For each and all of these reasons, discussed more fully below, the USPC should withdraw its proposed revisions with respect to BUD limitations in Chapters <795> and <797>, and update the BUDs that are a reflection of sound scientific evidence unabated by federal conjecture.

ARGUMENT

I. USPC'S REVISIONS TO GENERAL CHAPTER <797> HARM PATIENTS, DEPART FROM SCIENTIFIC CONSENSUS, AND UNJUSTIFIABLY BURDEN ESTABLISHED BUSINESSES

A. The Revisions To Chapter <797> Will Harm Patients

Most concerningly, the new BUD regulations for Chapter <797> threaten to harm patients because the shortened BUDs will interrupt established courses of therapy and disrupt prescribed regimens. At the same time, compounders will face daunting hurdles in trying to comply with the onerous, unprecedented demands imposed by the new standards. To the extent that certain compounders are ultimately able to come into compliance (as not all can, and none can right away), the upshot under the best of circumstances will leave patients facing tougher access and pricing challenges than ever before, thereby making it more costly and difficult for patients to afford their prescribed CSPs and maintain compliance.

Below are a few illustrative examples of how the new BUD standards will undermine patient care:

- Progesterone 50 mg/ml injections are often on backorder and frequently necessary for fertility treatments. They are used to prevent possible miscarriages and pregnancy complications. Many pregnant women cannot tolerate other oral and/or vaginal therapies and need Progesterone in a timely manner and with a reasonable BUD to assist in

maintaining a healthy pregnancy. Shortened BUDs for Progesterone injections will, of course, make it more challenging for patients struggling with infertility to maintain their course of treatment, and likely require that they purchase more rounds, at more difficulty and higher cost. In addition, Progesterone is typically produced in multi-dose vials. Shortened BUDs would likely require single-use vials that will, in turn, unnecessarily increase the costs of this therapy.

- HCG 5000 units/ml is often prescribed for patients undergoing fertility treatments when the commercial Pregnyl is not available. If pharmacists cannot batch HCG in quantities permitted by longer BUDs, patients would be required to wait 48–72 hours for the injectable dose to be prepared. Yet patients who need HCG injections are often unaware of their need until the day of injection. For instance, they may undergo ultrasounds and bloodwork in the morning and discover the need for the HCG injection the same afternoon. The delay necessary to prepare the short-BUD injectable would mean that the treatment arrives too late in the patient's cycle to be effective.

- High-dose vitamin-C protocols are often used as an adjunct therapy for many cancer patients. Cancer patients who stand to benefit from high-dose vitamin C need to begin therapy as quickly as possible and need a preparation with the best-possible BUD dating to last the 10–12 week treatment cycle. Restrictive BUDs will increase the costs associated with producing compliant vitamin C protocols, thereby hindering patient access to critical cancer treatment.

- High-dose Methylcobalamin (PF) injections are often prescribed for patients with multiple sclerosis. Under the new BUD requirements, these therapies would be difficult to compound at a price and turnaround time that would not be prohibitive for patient access. Many veterans, for instance, require this medication to be promptly available upon request by their physician. The time required for proper dissolution of the API and compounding process would likely cause a large delay in turnaround time. If the cost of the preparation rises too high, veterans' insurance benefits will no longer cover the costs of the medication—making it difficult for veteran patients to receive the therapy they need.

- Shortened BUDs will also impact veterinary care and practice. For example, many veterinarians maintain an office supply of chloramphenicol ophthalmic ointment to treat dogs and cats suffering from bacterial conjunctivitis, which, unless treated properly, can lead to blindness. Under the new Chapters, chloramphenicol ophthalmic ointment, which is only available as a compounded formula, will have only a 30-day BUD. But a 30-day BUD for chloramphenicol ophthalmic ointment is impractical, at best, because, when accounting for the time the product will remain in the veterinarian's office before being prescribed, it is unlikely that the medication would last through the entire course of the patient's treatment—thereby forcing the patient either to purchase additional medication or to discontinue treatment altogether.

- Shortened BUDs will also adversely affect the increasing number of patients who receive sterile medications through the mail. Indeed, strict USP standards have reduced the number

of local pharmacies that can produce sterile compounded drugs. Because shipping these medications will typically add a week of processing, patients may not be able to take the entire thirty-day usage (one month supply) by the time it reaches the patient, — the period of usage will have been eaten into by the added shipping time.

- Many elderly or disabled patients depend on caregivers to pick up their medications. Often, these patients cannot afford to have their medications shipped to them. With the new BUD limitations, patients must now identify a caregiver to arrive at the pharmacy exactly the same day product sterility testing has finalized in order to maximize a thirty-day usage (one-month supply) before the BUD period runs. This is a significant burden to place on many elderly or disabled patients.

- Once the time required to conduct a conventional sterility test is considered, a patient who is prescribed a CSP stored at room temperature will be forced to choose one of two bad options: (i) wait at least two weeks to begin therapy in order to obtain a sterile preparation that, at best, needs to be discarded within thirty days of being dispensed; or (ii) begin therapy within a day with a sterile preparation that, at best, needs to be discarded within fourteen days. In either event, the likelihood of patients having delays and/or interruptions in medication therapy, particularly with long-term or maintenance therapy, is extremely high.

- Zoos, wildlife-management agencies, and other organizations that manage stocks of wildlife depend upon a steady supply of highly concentrated anaesthetics that can be delivered by remote dart injection. These formulations—usually of potent opiate agonists (etorphine, thiafentanil), less potent opiate agonists/antagonists (butorphanol tartrate), potent alpha-two agonists (medetomidine hydrochloride), benzodiazepine agonists (azaperone tartrate), and their respective antagonists (atipamezole, naltrexone)—must be immediately available whenever a medical or management need arises. They cannot be formulated on-demand. Restrictive BUD assignments will sharply limit the stock of CSPs these organizations can keep on hand. For instance, zoos depend on 10 mg/ml etorphine CSP. Under the revised BUDs, the CSP would remain usable for only about eighteen days after formulation and sterility testing. This means that zoos would have to replace their inventory of this critical drug every two-and-a-half weeks. For even the country's most established zoos, let alone the smaller ones, the additional expense that results may be prohibitive.

- The National Park Service, the Federal Fish and Wildlife Service, the U.S. Department of Agriculture, all fifty state wildlife management agencies, and tribal wildlife management groups all depend on these same drugs. But these agencies are responsible for research or herd management projects that involve large numbers of hoof stock under widely varying conditions. Variables like weather, personnel and equipment availability, and herd location affect when and how these drugs will be used—making it very hard to predict when the drugs will be administered. These drugs often must be called upon immediately, on an emergency basis, including when dangerous wildlife enter urban areas. If these essential CSPs must be used within eighteen days of formulation, unforeseeable events like a winter

storm could require that an agency dispose of and replace its entire CSP stock. Especially because many of these agencies operate under severe budget restriction, it is infeasible for them to be renewing an entire CSP supply on a regular basis.

The aforementioned examples are not meant to be comprehensive; rather, they simply illustrate some of the many ways in which the revisions to Chapter <797> will adversely and severely affect patients' health and disrupt the continuity and affordability of their care. There are thousands of other examples of drugs that will not be able to be produced or used as they should be consistent with the new BUDs. These alone are reasons why USPC should retract the proposed changes to Chapter <797>'s BUD standards. At the very least, USPC should provide alternative mechanisms for compounders to extend BUDs for CSPs.

B. The Revisions To Chapter <797> Depart From Scientific Consensus

By revising Chapter <797> so as to incorporate substantially shorted BUDs with no allowance to extend BUDs, USPC has blown past 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 Chapter <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.

Previously, Chapter <797> clearly correlated the risk of maintaining or achieving sterility with the conditions under which CSPs were prepared. As such, Chapter <797> allowed the assignment of longer BUDs to CSPs that are prepared under lower-risk conditions as compared to shorter BUDs assigned to CSPs prepared under higher-risk conditions. By implementing processes and controls that removed nonsterility risk factors, and by utilizing sterility tests simply as an incidental tool for confirming the effectiveness of these processes and controls, compounders were permitted to assign extended BUDs to CSPs to the extent practical for patient care, commensurate with the risk of nonsterility, and grounded in scientific evidence and testing. Now, however, under the revised chapter, all CSPs, regardless of the conditions under which they are prepared, are presumed to have a high risk of nonsterility, resulting in drastic shortening of BUDs assigned to all CSPs. The BUDs specified in the revised Chapter inexplicably and unfairly discount the more rigorous practice standards required throughout the rest of the Chapter—practice standards that appropriately require compounders to implement additional processes and controls that together ensure a very high likelihood of maintaining and achieving sterility. 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, as discussed below, have been arbitrarily established and no longer correspond with scientific indicators of sterility assurance.

First, scientific consensus does not suggest any need to shorten BUDs for CSPs that are not sterility tested. Whether or not sterility testing has been performed does not determine the

compounder's ability to achieve or maintain sterility of a CSP. Indeed, relying upon "end-product sterility testing" over and above the "sterilization process" itself is "without scientific foundation and can lead to erroneous conclusions." T.A. du Plessis, *The Shelf Life of Sterile Medical Devices*, 13 S. AFR. ORTHOPAEDIC J. 32, 33–34 (2014) ("It clearly follows that end-product sterility testing of a few medical devices following sterilization to 'demonstrate' or 'prove' that the entire batch is sterile, without a proper prior process validation, ***is without scientific foundation and can lead to erroneous conclusions*** with regard to the sterility of the batch as a whole. . . . ***Provided a properly validated sterilization process is used***, and the integrity of the packaging is maintained, there is ***no reason to limit the shelf life of a sterile medical device***—especially so in the case of radiation sterilization" (emphasis added)) (attached hereto as Exhibit A); *see also* Frances W. Bowman, *The Sterility Testing of Pharmaceuticals*, 58 J. PHARMACEUTICAL SCI. 1301 (1969) (attached hereto as Exhibit B).

If anything, USPC should be assigning less rather than more weight to sterility testing under Chapter <797>. Precisely because "sterility tests . . . have limitations," they "are not recommended as a component of a stability program for confirming the continued sterility throughout a product's shelf life or dating period." FOOD AND DRUG ADMIN., GUIDANCE FOR INDUSTRY: CONTAINER AND CLOSURE SYSTEM INTEGRITY TESTING IN LIEU OF STERILITY TESTING AS A COMPONENT OF THE STABILITY PROTOCOL FOR STERILE PRODUCTS 2 (2008) ("[S]terility tests for the purposes of demonstrating continuing sterility have limitations, with respect to the method's reliability, accuracy, and the conclusions that may be derived from the results. Because of the limitations of sterility tests described below, ***sterility tests are not recommended as a component of a stability program for confirming the continued sterility*** throughout a product's shelf life or dating period." (emphasis added)). Instead, what matters most is whether a compounder strictly adheres to best practices for establishing and maintaining a sterile environment, as other provisions of the USP recognize. *See* USP GENERAL CHAPTER <1211> STERILITY ASSURANCE ("CHAPTER <1211>") 8008 ("In a real sense, microbiological safety is achieved through the implementation of interrelated controls that in combination provide confidence that the items are suitable for use as labeled. ***It is the controls that provide the desired assurance from microbiological risk rather than the results of any in-process or finished goods testing.***" (emphasis added)). 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 BUD; 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.

Second, the BUD revisions are patently illogical when viewed in light of other provisions of Chapter <797> as well as the prior standards. For example, a low-risk level CSP under the prior version of Chapter <797> is equivalent, under the new standards, to a CSP prepared from only sterile starting components and processed aseptically. Under the old Chapter <797>, this type of CSP would be assigned the following BUDs:

STORAGE CONDITION	**BUD**
Room temperature	48 hours
Refrigerated	14 days
Frozen	45 days

Under the new Chapter <797>, this CSP can now be assigned the following BUDs:

STORAGE CONDITION	**BUD**
Room temperature	4 days
Refrigerated	10 days
Frozen	45 days

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. If USPC perceives a substantive basis for its puzzling, shifting reassessment of the relative sterility risks that have now become apparent at higher versus lower temperatures, it should specify what that basis is. As matters stand, we can find no basis.

The revisions are similarly confounding with respect to the impact of sterility testing itself. USPC is clear in its position that the revised BUDs are based on the risk of microbial contamination or failure to achieve sterility. *See* CHAPTER <797> § 14.3. Further, USPC states sterility testing of a CSP can provide additional assurance of the absence of contamination. *See id.* § 14.2. But the revised BUDs vary inexplicably in the assumptions they reflect about the ***relative impact*** of sterility testing on determining BUDs under a range of ordinary conditions. Consider the CSP above. The permissible BUD would vary thusly based on storage conditions and sterility testing:

STORAGE CONDITION	**BUD WITHOUT TESTING**	**BUD WITH TESTING**
Room temperature	4 days	30 days
Refrigerated	10 days	45 days
Frozen	45 days	60 days

These BUD assignments suggest that sterility testing alone decreases the sterility risk enough to allow an extra twenty-six days of storage for CSPs at room temperature. This same sterility test performed on the same CSP somehow reduces the sterility risk even more—by thirty-five days—if the CSP is refrigerated. When the same CSP is frozen, however, an identical sterility test seems to be far less effective in UPSC's estimation, as only an extra fifteen days of storage will be permitted. This scheme is mystifying, and, indeed, bizarre, by its own terms. USPC offers no explanation for its anomalous, inconsistent approach. If sterility testing in fact works ***better*** for ***refrigerated*** CSPs as compared to CSPs at ***room temperature***, only to become ***less*** effective for ***frozen*** CSPs, then USPC should have data or some other evidence that so indicates. But USPC has cited none so far as we are aware.

Additionally, because the time it takes to conduct a sterility test counts against a CSP's BUD, *see id.* § 14.1 tbl. 9 ("The BUD is determined from the date/time that preparation of the CSP is initiated."), sterility-tested CSPs' BUDs may be clipped even more drastically than Chapter <797> contemplates. Members of the Coalition have reason to believe that sterility testing a CSP

batch will take up to twenty days. If so, then the effective BUDs for the above-referenced CSP, if sterility tested, would be ten, twenty-five, or forty days, depending on storage conditions. Because this is only a marginal increase from the non-tested BUDs for this CSP, the revisions to Chapter <797> may have the perverse effect of *disincentivizing* sterility testing.

Other inconsistencies become glaring when comparing USPC's treatment of the effect of sterility testing on CSPs stored under the same conditions. For example, when it comes to an aseptically-processed CSP stored at room temperature, the sterility test alone decreases nonsterility risk enough to permit an extra twenty-six days of storage. *Id.* § 14.3, tbl. 11. In contrast, when it comes to a terminally-sterilized CSP that is also stored at room temperature, USPC treats the sterility test as reducing sterility risk that much further, permitting the BUD to be extended by thirty-one days. *Id.* Again, USPC has offered no justification for this differing treatment, nor can we discern any.

At the same time that the BUD revisions apply differing treatment to like CSPs, they fail to differentiate CSPs that are dissimilar in key respects. In particular, USPC has failed to distinguish between CSPs that are likely to support rapid proliferation of microbial growth—those that have a higher water activity ("Aw") and contain no antimicrobial preservatives—and those that are not (*e.g.*, petrolatum-based ophthalmic ointment) and/or contain antimicrobial preservatives. USPC has not even attempted to explain why the latter category would support the same rate of microbial proliferation as the former, thereby requiring equal limitation on BUDs.

At their core, the revised <797> BUD assignments rests 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***. To be sure, sterility testing may be a useful tool for confirming sterility and can be considered among other factors in setting the BUDs for CSPs. But it by no means follows that sterility testing alone should be taken, as USPC would now take it, as determining the likelihood that sterility has been achieved in a CSP. For instance, an aseptically processed CSP, stored at room temperature, that passes sterility testing, would now, under the revised Chapter <797>, be permitted a maximum BUD of 30 days. *Id.* A terminally sterilized CSP, also stored at room temperature, that does not undergo sterility testing would be permitted a maximum BUD of 14 days. *Id.* The revised Chapter <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. Nor is it plausible that USPC itself has come to that view.

Indeed, USPC's instant position ***directly conflicts*** with venerable, accepted principles of sterility assurance, including those reflected in ***other*** USP General Chapters:

- "Within the strictest definition of sterility, an item is deemed sterile only when it contains no viable organisms. However, this textual definition cannot be applied to actual items labeled as sterile because of irresolvable limitations in testing. Sterility cannot be demonstrated without the destructive testing of every sterile unit. In a real sense, microbiological safety is achieved through the implementation of interrelated controls that

in combination provide confidence that the items are suitable for use as labeled. ***It is the controls that provide the desired assurance from microbiological risks rather than the results of any in-process or finished goods testing***."" CHAPTER <1211> 8008.

- "Within the strictest definition of sterility, an article is deemed sterile when there is complete absence of viable microorganisms. *Viable*, for organisms, is defined as having the capacity to reproduce. Absolute sterility cannot be practically demonstrated because it is technically unfeasible to prove a negative absolute. Also, absolute sterility cannot be practically demonstrated without testing every article in a batch**.** ***Sterility is defined in probabilistic terms, where the likelihood of a contaminated article is acceptably remote.***" USP GENERAL CHAPTER <1116> MICROBIOLOGICAL CONTROL AND MONITORING OF ASEPTIC PROCESSING ENVIRONMENTS 7712.

- "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***." USP GENERAL CHAPTER <71> STERILITY TESTS 6407.

- "***Terminally sterilized products are the lowest risk category of sterile pharmaceutical products.*** Unlike products aseptically manufactured under conditions designed to prevent microbial ingress, terminally sterilized products are subjected to a sterilization process that imparts a quantifiable safety level. Terminal sterilization processes achieve this by delivering measurable physical conditions that correspond to microbial lethality. For terminally sterilized products, sterility assurance is defined in terms of the probability of nonsterility (PNS), or the probability of the terminal sterilization process generating a nonsterile unit (PNSU). Terminal sterilization processes must achieve a consistent validated performance of a PNSU of $\leq 10^{-6}$ (a probability of NMT 1 nonsterile unit in 1 million units produced)." CHAPTER <1211> 8010.

- "***Appropriately designed, validated, and controlled sterile product manufacturing systems are capable of exceptionally consistent performance*** in the preparation of products that have a probability of a nonsterile unit (PNSU) of $\leq 10^{-6}$. The exceptionally low probability of microbial presence in products manufactured using these systems renders the analytical methods described in STERILITY TESTS <71> statistically ineffectual." USP GENERAL CHAPTER <1222> TERMINALLY STERILIZED PHARMACEUTICAL PRODUCTS—PARAMETRIC RELEASE 8022.

In sum, by revising Chapter <797>'s BUD assignments as it has, USPC is effectively impugning the standards of practice it itself has established within Chapter <797>. *See* CHAPTER <797> § 14.3 ("The BUDs in Table 10 and Table 11 for CSPs are based on the risk of microbial contamination or not achieving sterility ***despite implementation of the requirements in this chapter***."). If USPC now believes the measures it has prescribed are somehow insufficient to ensure that batches of CSPs achieve statistical sterility, it should say so, and it should explain why. As for this Coalition, we continue to believe that USPC has gotten it right elsewhere: the right way to guard against sterility risks is by prescribing and following best practices for sterile

compounding in the first instance, and utilizing sterility tests simply to supply helpful confirmation. Whereas any sterility test will be limited to an isolated sample that may deviate from the remainder of a batch, the proper approach to sterile compounding should ensure sterility across an entire batch. That reality is well understood, and it has long been a cornerstone of Chapter <797>. We cannot fathom how or why USPC could have abandoned it.

So long as USPC continues to safeguard CSP safety by prescribing best practices in Chapter <797>, it should not go so far as to limiting BUDs to the point of making CSPs inaccessible to patients. If USPC has nevertheless come to the remarkable conclusion that it must drastically shorten BUDs to address identified safety risks that otherwise loom, then USPC is implicitly concluding that the requirements of Chapter <797> governing underlying compounding have proved ***inadequate*** to protect safety. Yet we have seen no evidence to show that the current USP standards have put patients at risk. If, nevertheless, this latter implication is what USPC intends to convey, then it should be overhauling Chapter <797> in ways that are far more profound. It would not remotely suffice for USPC simply to encourage sterility testing or to shorten BUDs, neither of which would be a satisfying substitute for prescribing a sound approach to sterile compounding across the board.

We consider USPC's revision fundamentally misconceived and do not understand what drove such a drastic change. If the standards in Chapter <797> are designed and operating as they should, then USPC has no justification for massively and arbitrarily shortening BUDs, or for ignoring the scientific data that have hitherto properly determined BUDs. If, on the other hand, the standards are not operating as they should, then USPC should be addressing any underlying sterility problems head-on and prescribing compounding practices that will solve them at their source. In no event should sterility testing be treated as the be-all, end-all.

C. The Revisions To Chapter <797> Will Unjustifiably Burden Established Businesses

Beyond inflicting harm on patients and neglecting a corpus of scientific evidence to the contrary, the revisions will also unjustifiably harm established businesses. Compounders will now face tremendous difficulties and expenses in trying to comply with the onerous, unprecedented demands imposed by the new standards, all without any corresponding benefit to the health or safety of patients. The new BUD rules burden the industry in two basic ways. First, compounders will be forced to produce smaller CSP batches more often in order to meet patient needs, increasing the cost to make each CSP unit. Second, these shortened BUDs will not allow compounders to make adequate amounts of CSPs far enough in advance of receiving prescriptions to be able to meet the needs of patients on aggregate. Higher costs and an inability to consistently serve patients will harm compounders (and, by extension, medical practices and patients) in several ways.

Because the unit cost of CSP preparation does not closely correspond with batch size, it will necessarily cost more for compounders to produce more, smaller batches rather than fewer, larger batches. Because approximately 40% of the cost of producing CSPs is fixed, costs will rise precipitously as compounders try to meet their patients' therapeutic needs in less efficient ways. For instance, a six-day supply of cyclosporine in corn oil 2% ophth. 15 ml, which can currently be

filled in a batch size of 1216 units, costs $1.96. Under the new BUD standards, the same supply of the same CSP could only be fulfilled in in a batch size of 501 units—and it would cost $3.14, a 37.5% increase. By imposing arbitrarily short BUDs, the new Chapter <797> will require all compounders to produce in smaller quantities, with cost and safety alike rendered irrelevant to the equation. The resulting costs will be gratuitous and substantial—borne first by compounders and then, inevitably, patients, as pharmacies struggle to cover the inflated costs resulting from the new standards.

Relatedly, the shortened BUDs will also likely generate massive amounts of potentially hazardous pharmaceutical waste. Take, as just one example, apomorphine—a drug used by veterinarians to induce vomiting in poisoned pets. Virtually all veterinarians keep an office supply of apomorphine on site for emergency situations. If apomorphine has a reduced shelf life as a result of shortened BUDs, practitioners will be forced to dispose of and reorder apomorphine if the product is not used prior to the expiration of the BUD. Such waste is, however, entirely unnecessary given that there is proven science and testing to show that these medications are still suitable for administration well beyond the arbitrarily shortened BUDs. Even the USP's own monographs establish that many CSP can be safely used long after the arbitrarily short BUDs of Chapter <797> have run. For instance, a USP monograph provides that sodium phosphates compounded injections, if sterility tested, have a maximum BUD of 120 days when stored at room temperature. UNITED STATES PHARMACOPEIA, OFFICIAL MONOGRAPHS—SODIUM 1. By contrast, under the revisions to Chapter <797>, this same CSP, even if sterility tested and terminally sterilized, would be assigned a BUD of only forty-five days at room temperature. CHAPTER <797> § 14 tbl. 11. The same holds for other compounds: Despite the existence of established monographs setting reasonable BUDs, the revisions to Chapter <797> will mandate artificially short BUDs. *Compare, e.g.*, UNITED STATES PHARMACOPEIA, OFFICIAL MONOGRAPHS—DEXAMETHASONE 1 (dexamethasone sodium phosphate compounded injection), MORPHINE 1 (morphine sulfate compounded injection), POTASSIUM 1 (potassium phosphates compounded injection), SODIUM 1 (sodium bicarbonate compounded injection), *with* CHAPTER <797> § 14 tbl. 11. Again, these are just a few of many similar examples.

The new standards will increase costs in still other ways. They will require pharmacies to both perform their ordinary sterilization and safety regimens more often (to accommodate an increase in the number of batches they produce), and to spend more per unit on each test. For instance, sterility testing costs approximately $150 for a batch of a typical CSP. If a CSP batch size decreases from fifty units to five units as a result of the shortened BUDs, the testing cost per unit increases from $3 to $30—and to produce fifty units, the producer now needs to conduct ten tests instead of one. In addition, sterility testing takes up valuable time—time better spent providing high quality CSPs to patients. A compounder utilizing an outside testing lab to perform sterility testing will on average receive test results twenty days after the CSP has been produced. As noted above, this delay in the availability of the CSP will not only delay or interrupt essential medical treatment, but also overburden producers. One coalition member, Wedgewood Village Pharmacy, estimates that under the new BUD standards, it would need to double its spending on labor and sterility testing, and increase its expenditure on sterile compounding supplies by 40%. In total, Wedgewood would need to increase its annual spending by over one million dollars.

In addition, the massive investment pharmacies have made in establishing the scientific basis for specific BUDs as to specific CSPs will be squandered. Those established BUDs will be jettisoned and foreclosed without regard for the relevant science. And compounders will have received an unsettling message that their efforts and expenditures to comply scrupulously with a regime established by USPC will prove to be for naught in the event that USPC changes whims.

To be sure, financial and logistical burdens should rightly and necessarily be borne when appropriate measures are being taken to benefit patients. This Coalition so recognizes, and has no inclination or penchant to push back when new rules are suggested to improve patient safety, whatever the attendant expense. But the circumstances here are quite different. Because the new BUD rules lack any discernible scientific basis, this slew of new costs will be wholly unjustified, needlessly burdening pharmacies, practices, and patients alike to the ultimate detriment of patients. This unnecessary extra cost and work will strain the already limited personnel and financial resources of many compounders who want to be focusing instead on quality and safety. Worse still, patient safety stands to suffer. Shortened BUDs may well lead to a decrease in the standardization of compounding protocols as pharmacies scramble to produce more batches of CSPs. In this way, the burdens imposed by Chapter <797> may increase the risk of error and oversight in preparing CSPs. Any such risk should be avoided—especially where USP is purporting to advance the safety and reliability of sterile compounding yet no evidence suggests it will achieve that purpose and there are strong indications that it is doing precisely the opposite.

Our substantive concerns are exacerbated by recognition that the new standards will have a profound and far-reaching impact, ostensibly far beyond what USPC appreciates. The Coalition have determined that an estimated 91% of the CSPs they or their member organizations make will be assigned shorter BUDs under the new regime—with the average BUD for CSPs being shortened by up to five months. Among the CSPs most affected are common preparations of tacrolimus and cyclosporine ophthalmic used to treat KCS in dogs and other inflammatory/autoimmune diseases in humans, as well as methylcobalamin used to treat vitamin B12 deficiencies. We believe it is imperative that USPC reckon with the magnitude of the revision's impact and immediately withdraw the BUD provisions.

Indeed, even if the revisions to the Chapters were otherwise sound (notwithstanding the avalanche of contrary comments and points made herein), there simply is no way that compounders could be expected to come into compliance by December 1 of this year. USPC is shifting the ground underneath the entire industry responsible for sterile compounding. Only by making fundamental changes—requiring corresponding investment, budgeting and planning—to such things as facilities, staffing, logistics, protocols, and pricing can compounders hope to overhaul their existing approach to arriving at CSPs so as to comply with the new guidelines. To the extent that compounding pharmacies are able to make the required changes (and many, particularly smaller pharmacies, will not), it will take many more months for them to do so. Indeed, it is altogether unfair and unrealistic under even the most optimistic scenario to expect compliance with the new guidelines any time before December 2020, well after the December 2019 effective date currently contemplated. As such, USPC will need to not only update BUDs, but also allow for adequate time for all industries affected by these revised BUDs to comply.

II. USPC'S REVISIONS TO GENERAL CHAPTER <795> DEPART FROM SCIENTIFIC CONSENSUS

The Coalition also objects to the BUD changes promulgated in the proposed Chapter <795>. As with the changes to Chapter <797>, the Chapter <795> revisions impose harsh and arbitrary limits that will harm patients and are unsupported by scientific evidence.

First, there is no scientific rationale for assigning different BUDs to solid dosage form CNSPs and nonaqueous dosage form CNSPs. Specifically, Table 3 in the new Chapter <795> specifies a ninety-day maximum BUD for nonaqueous dosage forms and a 180-day maximum BUD for solid dosage forms. USP GENERAL CHAPTER <795> PHARMACEUTICAL COMPOUNDING—NONSTERILE PREPARATIONS ("CHAPTER <795>") § 10.3 tbl. 3. But we are aware of no scientific basis for why the new Chapter <795> provides a shorter maximum BUD (ninety days) for nonaqueous dosages like suppositories, ointments, fixed oils, and waxes compared to the allowable maximum BUD for solid dosages, like capsules and tablets (180 days). At best, USPC might purport to base its distinction on variations in water-activity levels between nonaqueous and solid dosages. Such a rationale would, however, be misguided. Many nonaqueous dosage forms and solid dosage forms have equivalent water-activity levels. As reflected in Chapter <1112>, vaginal and rectal suppositories and lip balm (*i.e.* nonaqueous dosages) have the same or lower water-activity levels than solid dosages, like compressed tablets and liquid filled capsules. *See* USP GENERAL CHAPTER <1112>—APPLICATION OF WATER ACTIVITY DETERMINATION TO NONSTERILE PHARMACEUTICAL PRODUCTS 35, tbl. 2. As such, the differences in water-activity levels simply cannot account for the massive variance between the ninety-day BUDs for nonaqueous dosages and the 180 BUD for solid dosages.

Second, Chapter <795> permits BUDs for certain CNSPs to be extended up to maximum of 180 days if there is a supporting stability-indicating study. In many instances, however, these stability studies demonstrate that the CNSPs are actually "stable" (as that term is defined in Chapter <1191>)[1] well ***beyond*** the maximum 180 days prescribed by the new Chapter <795>. Despite the fact that the scientific testing establishes "stability" beyond 180 days, Chapter <795> limits the BUDs to a maximum of 180 days. There is simply no scientific rationale for limiting the BUD for CNSPs that have undergone stability-indicating studies to 180 days when those studies indicate the CNSP will be stable for longer. To the extent USPC perceives basis to trump what the data show about the stability of a CNSP, it should be specifying and substantiating its perceived basis. We would urge USPC, however, to stick with the relevant science and let that determine the relevant BUD.

[1] Chapter <1191> defines "stability" as "the extent to which a product retains, within specified limits, and throughout its period of storage and use (i.e., its shelf-life), the same properties and characteristics that it possessed at the time of its manufacture." USP GENERAL CHAPTER <1191> STABILITY CONSIDERATIONS IN DISPENSING PRACTICE 35.

III. THE REVISIONS TO GENERAL CHAPTERS <795> AND <797> WERE PROCEDURALLY DEFICIENT

In addition to the glaring substantive deficiencies of USPC's revisions to the Chapters, there are two separate and distinct aspects of USPC's structure and procedures that raise legal concerns as relevant to this appeal.

First, as a threshold issue, the incorporation of USPC into federal law under the FDCA violates Article I, Section I of the U.S. Constitution, which prohibits Congress from improperly conferring lawmaking authority on other bodies—especially private entities, like USPC. *See A.L.A. Schechter Poultry Corp. v. United States*, 295 U.S. 495, 529 (1935) (holding that "Congress is not permitted to abdicate or to transfer to others the essential legislative functions with which it is thus vested"). For this reason alone, USPC and its corresponding standards are constitutionally suspect.

Second, even if the role USPC plays in federal law were constitutionally permissible, USPC has failed to meet the procedural requirements of federal law that are properly imposed upon it as it effectuates state action driven and backed by FDA. For this additional reason, too, USPC cannot stick with its current proposals—or else, if it does, it should expect them ultimately to be set aside by a reviewing court as procedurally defective.

Again, it bears emphasizing that the Coalition's substantive concerns are what lead the Coalition to raise these procedural concerns. In the face of unjustified, nonscientific revisions that threaten an entire industry and all the patients and practitioners who rely on it, we have no choice but to note the ways in which USPC's relevant composition and process are legally defective, and to reserve all legal rights on behalf of the Coalition and its members.

A. <u>USPC's Purported Authority To Act As A Private Standards-setting Organization Is Unconstitutional</u>

Congress holds sole constitutional power to legislate for the federal government. Agencies hold interstitial authority to regulate for the federal government. But private entities have no authority whatsoever to interject themselves into the federal lawmaking equation, as USPC has been doing. This whole arrangement should be held unconstitutional by any court that may be duly confronted with the question.

Article I, Section I of the U.S. Constitution provides that "[a]ll legislative Powers herein granted shall be vested in a Congress of the United States[.]" U.S. CONST. art. 1, § 1. From that constitutional bedrock comes the non-delegation doctrine, which prevents Congress from farming its Legislative Power out to anyone or anything outside of the Legislature. Even when Congress wants to provide statutory authorization for an agency within the Executive Branch to regulate, therefore, Congress is constitutionally constrained to do so pursuant to an "intelligible principle"—that is, a clear prescription for how its delegated authority is to be used. *See Whitman v. Am. Trucking Ass'ns*, 531 U.S. 457, 472 (2001). When Congress fails to provide any "guidance for the exercise of discretion," it has failed to offer an "intelligible principle" and any attempted delegation

of legislative authority, even within the federal government, is unconstitutional. *Id.* at 474 (citing *Panama Refining Co. v. Ryan*, 293 U.S. 388, 415 (1935)). The situation here is obviously much worse: Not only is USPC wielding vast legal power unconstrained by any intelligible principle, but it is doing so under private auspices outside the constitutional umbrella of the United States.

In incorporating USPC into federal law via the FDCA, Congress appears to have conferred upon USPC virtually unbridled, unreviewable authority to change and, indeed, overhaul, federal law regulating pharmacy drugs and practice, including as to compounded formulas. Specifically, Congress has delegated to USPC the power to determine what qualifies as a "drug" under federal law and what standards a "drug" must meet to avoid criminal prosecution for adulteration or misbranding. *See, e.g.*, 21 U.S.C. § 321(g)(1), 21 U.S.C. § 351(b), 21 U.S.C. § 352(g). More generally, the FDCA provides that when a drug is recognized by the USP, "it shall be subject to the requirements of the United States Pharmacopeia." 21 U.S.C. § 351(b). Moreover, the FDCA incorporates all future revisions to USPC's standards. *See* 21 U.S.C. §321(j). As a result, USPC wields extraordinary authority to alter what qualifies as a drug under federal law and to modify the laws governing drug compounding throughout the United States. *See* 21 U.S.C. §331(a)(b)(c); 21 U.S.C. §333 (forbidding conduct by reference to terms USP has power to define). In other words, by incorporating USPC's standards into federal law; Congress has created pharmaceutical standards the violation of which could land someone in prison.

USPC wields its lawmaking powers free from any meaningful government oversight. The FDCA contains no language to guide or constrain how or why USPC is to arrive at a particular regulation. Nor does the FDCA purport to authorize FDA (or any other government entity) to modify or veto whatever additions or revisions USPC may adopt as its chosen standards. By all indications, USPC has complete, unbridled discretion to define the scope and substance of federal law in a crucial area of regulation so as to hold sway over entire industries—industries that are essential to medical patients and care throughout the country—without any meaningful governmental oversight. For this reason alone, USPC and its corresponding standards should be held unconstitutional, if ever put to the test in court.

Notably, at least one federal court has recently recognized the constitutional concerns regarding USPC's incorporation into federal law. *See United States v. Cadden*, No. 14-10363, 2016 WL 1948832, at *1 (D. Mass. May 3, 2016). In the context of that criminal prosecution, the Court observed:

> that the references to the USP in the FDCA are "patchy" and unsystematic, that ***no guidance*** is provided directly by Congress (or indirectly through the [FDA]) to the USP's Expert Committees, that the FDA has ***no discretion*** to accept or reject the revisions made in the USP, and that the FDA has ***no oversight authority*** over the USP, only permission from Congress to "cooperate" with it in the making of revisions to the USP.

Id. at *7 (emphases added). In *Cadden*, the Court was able to avoid ruling on the precise constitutional question, because the United States disavowed any reliance on USP standards for purposes of the prosecution there and the Court foreclosed the jury from considering USPC's

standards. *See id.* at *8. Even so, the Court went out of its way to note the non-delegation problem posed by the incorporation of USPC's standards into federal law and to rule that USPC's standards could not properly serve as a touchstone for the prosecution. *Id.*

Setting aside the absence of the requisite "intelligible principle," USPC's role would be patently unconstitutional for a more fundamental reason. Congress is ***altogether forbidden*** from delegating its legislative power to ***any*** private entity, as it has done here by enlisting USPC to define and revise federal law on an ongoing basis. The D.C. Circuit specifically so held in a 2013 opinion that considered the role played by Amtrak. *See Ass'n of Am. Railroads v. U.S. Dep't of Transp.*, 721 F.3d 666, 668 (D.C. Cir. 2013), *vacated on other grounds and remanded sub nom. Dep't of Transp. v. Ass'n of Am. Railroads*, 135 S. Ct. 1225 (2015). In *Amtrak*, the Could held that "***[f]ederal lawmakers cannot delegate regulatory authority to a private entity***." *Id.* at 670 (emphasis added). As the D.C. Circuit stated, assigning regulatory authority to a private party is "***legislative delegation in its most obnoxious form***." *Id.* (emphasis added) (citing *Carter v. Carter Coal Co.*, 298 U.S. 238, 311 (1936)). In reaching its conclusion, the court expressly recognized that "even an intelligible principle cannot rescue a statute empowering private parties to wield regulatory authority." *Id.* at 671. Thus, even if Congress has provided USPC with an "intelligible principle" with which to wield its quasi-legislative powers (and Congress has not), such a delegation of power would be *per se* unconstitutional.

B. USPC's Standards-Setting Procedures Fail To Provide Legally Required Procedural Protections

Assuming USPC would try to defend its power over federal law by contending it operates as a *de facto* extension of the federal government, it would necessarily follow that USPC is, at a bare minimum, bound by the same legal constraints that any other arm of the federal government is. By that theory, too, a legal defect becomes apparent: USPC's standards-setting procedures violate both the Due Process Clause of the Fifth Amendment to the U.S. Constitution and the APA.

1. USP Is Bound By And Violating Due Process

According to the United States Constitution, "No person shall be . . . deprived of life, liberty, or property, without due process of law." U.S. CONST. amend. V. The Due Process Clause protects specifically against deprivations by state actors. To the extent USPC is not a creature of the government, it has no basis to be regulating for the government, as already explained. To the extent that USPC is nonetheless wielding governmental powers, the best it could hope to establish is that it is a legitimate extension of the government—*i.e.*, a state actor. Absent any other constitutional impediment, therefore, USPC should be recognizing its obligation to abide by the Due Process Clause and conducting itself accordingly.

A private entity such as USPC qualifies as a state actor if the government "participat[es]" in its activities, putting "its power, property and prestige behind" the entity, or when there is "interdependence" between the entity and the state. *Burton v. Wilmington Parking Auth.*, 365 U.S. 715, 722, 725 (1961). The relationship between USPC and the FDA answers to both definitions.

Indeed, FDA's relationship with USPC is codified in federal law. *See* 21 U.S.C. § 377 ("The Secretary, in carrying into effect the provisions of this chapter, is authorized . . . to cooperate with associations and scientific societies in the revision of the [USP][.]"). This alone makes USPC a state actor for purposes of constitutional analysis. Similarly, regulations of state bar associations can be challenged under the Constitution once incorporated into state law. *See Fla. Bar v. Went For It, Inc.*, 515 U.S. 618, 622 (1995); *see also Bates v. State Bar of Ariz.*, 433 U.S. 350, 360–61 (1977).

Beyond this authorization of federal involvement with USPC, the actual interdependence between FDA and USPC confirms USPC's status as a state actor. This interdependence jumps out upon reviewing USPC's literature and publications that emphasize USPC's extensive collaboration with FDA. *See* UNITED STATES PHARMACOPEIA, USP AND FDA WORKING TOGETHER TO PROTECT PUBLIC HEALTH (2018). By USPC's account, there are multiple "established channels" that inextricably link USPC to FDA, including that:

- "Five FDA centers and the Office of the Commissioner have established delegates at USP's Convention, the [USPC's] top leadership body";

- "USP staff maintain executive-level contacts with FDA leadership and routine contacts with FDA's Compendial Operations and Standards Branch through quarterly meetings";

- "More than 100 FDA staff participate as government liaisons on USP's Expert Committees and Expert Panels, the scientific bodies that develop and revise USP's written and physical standards."

- "FDA and USP work together to identify areas for monograph or general chapter development . . . ."

Id.

USPC has gone so far as specifying that FDA officials work with it in their official capacities: "***Government liaisons represent FDA opinions and viewpoints*** (as opposed to other USPC volunteers, who represent their own opinions rather than their employers') at public USPC meetings such as the Expert Committee Meetings, Expert Panels and Stakeholder Forums." *Id.* And USPC calls its relationship with FDA an "essential" part of its work. *Id.* Consistent with that, USPC recently adopted a corporate resolution for the avowed purpose of "***increas[ing] communication and collaboration with the [FDA] to promote alignment with FDA's regulatory and scientific policies from the inception of the standards planning and development process***." UNITED STATES PHARMACOPEIA, 2018 STATUS OF THE USP RESOLUTIONS, RESOLUTION I: COLLABORATION WITH THE U.S. FOOD AND DRUG ADMINISTRATION – TRANSCRIPT (emphasis added). Further to the collaboration between USPC and FDA, USPC has expressly "committed to continue engaging with FDA and to explore other mechanisms ***to enhance our collaboration on important quality issues and ways that USP can leverage its public standards-setting process***." *Id.* (emphasis added).

The whole point of this extensive, intensive, thoroughly documented collaboration between USPC and FDA is to ensure that USPC's development of pharmaceutical standards aligns with the federal government's interests and views. In a real sense, USPC has designed and oriented itself to do the bidding of FDA and to guard against any divergence from the regulatory blueprint drawn up by FDA. As best we can tell, USPC is constantly asking the question "what would FDA want us to do?," looking to FDA for the answer, and adjusting its compass accordingly. There is no way to escape the conclusion that USPC has thereby made itself a state actor that regulates as an extension or proxy of FDA. As such, USPC no less than FDA should be subject to the Due Process Clause, by even the most permissive account. Yet USPC is not affording due process.

The U.S. Supreme Court has emphasized that the "fundamental requirement of due process is the opportunity to be heard 'at a meaningful time and in a meaningful manner.'" *Mathews v. Eldridge*, 424 U.S. 319, 333 (1976) (quoting *Armstrong v. Manzo*, 380 U.S. 545, 552 (1965). Here, USPC's efforts to revise Chapters <795> and <797> failed to provide Coalition members (among others) with fair opportunity to be heard in a meaningful manner, free from arbitrary decision-making or bias. Although USPC invited comments in response to its proposed revisions, USPC ignored scientific authority and reasoned comments and concerns submitted by Coalition members whose businesses and/or patients stand to be impacted by USP's proposed changes. Of the untold numbers of comments submitted on General Chapter <797>, the Pharmacy Compounding Expert Committee seems to have rejected most all of them out of hand, offering at most conclusory assertions to the effect that the adopted text was supported by scientific evidence, without meaningfully addressing competing concerns. *See* UNITED STATES PHARMACOPEIA, COMMENTARY, USP 42–NF 37, SECOND SUPPLEMENT § 14 (2019).

Nor is USPC constituted to afford due process. Many of its crucial standards-setting operations and procedures are shrouded in secrecy. For example, although USPC purports to provide "general information pertaining to standards-setting" available to the public, USPC has, nonetheless, carved out a critical limitation to its public disclosure obligations. UNITED STATES PHARMACOPEIA, CODE OF ETHICS 7–8. Specifically, USPC will not provide to the public any "communications of any kind among or between USP staff and members of the Board of Trustees, Council of Experts, or Expert Committees." *Id.* at 8. As a result, USPC can shield from public disclosure critical information about its standards-setting process despite the immense public importance and interest that process carries.

Similarly, although USPC purports to welcome public participation in its meetings, USPC has again carved out a key limitation that allows the organization to close meetings involving the "review or discussion of matters whose premature disclosure could be detrimental to USP's standards-setting activities." *Id.* That catch-all affords a virtual blank check for USPC to shroud its standards-setting process in secrecy. Tellingly, while USPC closes such meetings to the public, it nonetheless allows representatives of ***FDA*** "to participate in confidential discussions during an Expert Committee or Expert Panel meeting." UNITED STATES PHARMACOPEIA, RULES AND PROCEDURES OF THE 2015–2020 COUNCIL OF EXPERTS ("RULES AND PROCEDURES") § 6.02. FDA is, therefore, invited to inject its views, inputs, and agendas behind the scenes of USPC, without the public knowing how or why FDA is pulling the strings.

Notably, neither USPC's Bylaws nor the Rules and Procedures of the Council of Experts commit definitively to what procedures or standards USPC must follow when revising its General Chapters. *See generally* RULES AND PROCEDURES § 7. As a result, USPC is left to its own devices (unchecked by Congress or the courts) to decide, on a case-by-case basis, when, how, and under what circumstances it will make changes to its standards—standards that then effectively have the force and effect of federal law and trigger criminal penalties for violations. It is all too predictable that such plenary, unbridled authority would lead to arbitrary and surprising changes to federal law (*i.e.* the FDCA) of the sort that have occasioned this appeal. Such a state of affairs offends fundamental fairness and due process as long cherished in this country. *See Holmes v. N.Y.C. Hous. Auth.*, 398 F.2d 262, 265 (2d Cir. 1968) (finding that "the existence of an absolute and uncontrolled discretion in any agency of government vested with the administration" of a government program would invite intolerable abuse); *see also Carey v. Quern*, 588 F.2d 230, 232 (7th Cir. 1978) ("In the context of eligibility for welfare assistance, ***due process requires at least that the assistance program be administered in such a way as to insure fairness and avoid the risk of arbitrary decision making***.") (emphasis added).

2. USPC Is Bound By And Violating The APA

Relatedly, USPC's standards-setting procedures fail to satisfy important, well-established strictures of the APA. In order to safeguard due process, the APA governs, *e.g.*, how "agencies" of the United States are to develop and issue regulations, rules, and guidance, including through the notice-and-comment process that traditionally defines public rulemaking. *See* 5 U.S.C. § 553. Although the APA typically applies only to governmental "agencies" (like the FDA), entities like USPC that function as a federal agency or agent thereof are also required to follow the APA's requirements. *See Soucie v. David*, 448 F.2d 1067, 1073, 1075 (D.C. Cir. 1971) (holding that a state actor is an "agency" when it exercises an "independent function" of evaluating federal scientific programs). Again, USPC is directly and uniquely shaping federal law and policy concerning the use, development, and distribution of pharmaceuticals—a role that is either reserved for the government, or else must be subject to the same constraints imposed upon the government. There should be no way, however, for USPC to regulate as it does without satisfying the requirements the APA places on regulators. Yet USPC has violated those requirements as well.

In purporting to promulgate new or revised standards, USPC should be adhering precisely to the APA's rules regarding notice-and-comment rulemaking. Under these rules, USPC is required to issue notices of proposed standards-setting, publish notice of meetings, issue draft standards, solicit and incorporate comments, and then respond substantively to each. *See* 5 U.S.C. § 553. USPC has failed to meet these notice-and-comment requirements. For one, although the Pharmacy Compounding Expert Committee reviews comments responsive to proposed revisions, it is not required to provide a rationale for adopting or rejecting a comment. *See* RULES AND PROCEDURES § 7.05(c) (mandating only that the USPC provide "succinct response[s]" to comments). This contrasts with federal law, which requires agencies to offer reasons why comments were adopted or rejected. *See* 5 U.S.C. § 553(c). Nor does USPC publish the comments that it receives from interested parties or otherwise make them readily available to the public or other interested stakeholders, as FDA typically does when it requests public comments. *Compare,*

e.g., RULES AND PROCEDURES § 7.05(c), *and* CODE OF ETHICS 6, *with* Generic Drug User Fees; Public Meeting; Request for Comment, 80 Fed. Reg. 22,204, 22,204 (Apr. 21, 2015) (pledging to "publish the comments" responsive to possible legislative action), *and* Medical Device User Fee Act; Public Meeting; Request for Comments, 75 Fed. Reg. 49,502, 49,502 (Aug. 13, 2010) (same).

Most importantly, USPC's cursory and conclusory dismissal of virtually all the opposing comments it received relating to BUDs falls short of the reasoned, transparent, responsive decision-making that the APA demands of a federal agency propounding any such rule. USPC's standards should be based on a record demonstrating rational, evidence-based scientific justifications. *See e.g.*, 5 U.S.C. § 706(2)(A); *Motor Vehicles Mfrs. Ass'n of the United States v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983) ("[T]he agency must examine the relevant data and articulate a satisfactory explanation for its action[.]"). Additionally, USPC would be required to publicly articulate its rationales. *See e.g.*, 5 U.S.C. § 552(a); 5 U.S.C. § 552b; 5 U.S.C. 553(b). USPC's recent revisions to the Chapters do not come close to satisfying these established standards. To the contrary, the revisions exemplify what federal courts have deemed arbitrary and capricious under the APA: They fail to account for the extensive comments provided to USPC by members of the Coalition, which demonstrated that the revisions lacked scientific consensus and would damage patient health and safety.

For example, one Coalition member raised concerns in its comments—echoed in this appeal—about the key role sterility testing plays in the new BUD assignment scheme. The Coalition member demonstrated the lack of scientific consensus supporting the paramount importance the revision placed on sterility testing, the tension the new BUD rules would create with other USP standards on sterility best practices, and the disastrous practical consequences that the revised standards would bring. USPC responded only thus: "Comments not incorporated. Sterility testing offers additional rigorous and scientifically justified assurance that a CSP is sterile." UNITED STATES PHARMACOPEIA, COMMENTARY, USP 42–NF 37, SECOND SUPPLEMENT § 14 (2019). This cursory, conclusory statement did not cite any scientific authority, nor did it offer even a cogent explanation of *why* the comment was rejected. The same dynamic—perfunctory, unsupported responses to thoughtful, detailed submissions—recurred across other comments submitted by this Coalition member.

In sum, rather than consider these detailed and empirically-based comments, USPC cast them aside (without so much as engaging them substantively) in favor of its own unsupported say-so. Even if USP's Bylaws and the Rules and Procedures do not demand that supporting scientific evidence be marshaled to overcome scientific objections to a new or revised standard, the APA most certainly does. Just as USPC in this instance is not answering to science or to reason, neither is it answering to law and the requirement of reasoned decision-making. Its adoption of the new guidelines is incapable of withstanding scrutiny under the APA.

We believe that USPC's standards should, if they persist in their current form, be reviewed and vacated by a federal court. The APA affords judicial review to any person "adversely affected or aggrieved" by an agency's actions. 5 U.S.C. § 702. In contrast, Article VII, Section 7 of USPC's Bylaws provides a procedurally opaque and ill-defined process for "appeals." Specifically, it states that "[t]he Council of Experts shall adopt rules and procedures for appealing

any standard adopted by the Council." UNITED STATES PHARMACOPEIA, 2015–2020 USP BYLAWS, art. VII, § 7. But no such rules or procedures are publicly available. Instead, the Bylaws provide only a skeletal timeline for processing appeals, without illuminating how appeals are resolved, or under what legal or scientific standard appeals they are to be considered. The Rules and Procedures of the Council of Experts similarly provide only that a submitted appeal "shall specify the grounds for the appeal and contain appropriate supporting documentation." RULES AND PROCEDURES § 7.08. For those (like the Coalition) that seek to challenge USP standards as suspect and problematic, these instructions provide little to no guidance or direction as to how an appeal is meant to be pursued and decided, in process and in substance. In short, the appeal process contemplated by USPC's Bylaws is no substitute for the right to judicial review in federal court under the APA. The deficiencies in this process make it all the more imperative that the Coalition be clear with all concerned that it is reserving all rights, even as it makes good-faith efforts to obtain satisfying resolution through USPC's current appellate process.

Finally, the absence of transparency and public accessibility that afflicts USPC is inimical to how a federal agency is meant to conduct itself, particularly under the Freedom of Information Act. *See, e.g.*, 5 U.S.C. § 552(a). Whereas a federal agency is meant to be inviting public engagement and inquiry, USPC provides only limited opportunities for public engagement and review of its work. For example, as mentioned above, although USPC purports to make certain internal information available for public disclosure, USPC has shielded a substantial and critical set of communications from those disclosure obligations—namely, the all-important internal communications between and among its Council of Experts and Expert Committees. *See* CODE OF ETHICS 6. This limitation is particularly disconcerting because USPC permits FDA employees to serve on its Council of Experts and Expert Committees. RULES AND PROCEDURES § 6.03. By permitting FDA employees to moonlight on USP Expert Committees or the Council of Experts, USPC can effectively shield from public disclosure external communications with FDA staff, which external communications with FDA seem likely to be dispositive. To say that ***other*** aspects of USPC's proceedings are public is unsatisfying, at best, and potentially meaningless.

While the Council of Experts provides for Advisory Stakeholder Forums, it does not guarantee stakeholders a voice in its decision process or specify what these Forums are able to do. *See generally* RULES AND PROCEDURES § 9. And while the Council of Experts generally maintains open meetings, the Chairperson may close a meeting to the public at his or her whim. *See* RULES AND PROCEDURES § 10.01(a). What is worse, USPC can, notwithstanding the fact that the meetings are otherwise closed to the public, invite and include staff members from FDA in these meetings for their input and analysis. *See* RULES AND PROCEDURES § 6.02. As a result, FDA is free to provide commentary behind the scenes, shielded from public scrutiny and criticism. Further shrouding USPC in secrecy is the process by which Expert Committee members vote on the approval of new standards. As written, USPC's Rules and Procedures appear to authorize the use secret ballots when voting on new standards. *See* RULES AND PROCEDURES § 7.06(a). Secret ballots, of course, lead to a total lack of transparency in terms of how each committee member—several of whom may have day jobs that pose ostensible conflicts of interest—voted with respect to the adoption of new standards. Such furtive decision-making would not be permitted under the APA, and USPC should not be permitted to circumvent the APA while serving as FDA's proxy.

CONCLUSION

For all of the reasons set forth above, USPC's standards-setting procedures are deficient and its resultant standards, which are presently set to go into effect on December 1, 2019, are due to be set aside. The Coalition therefore respectfully requests that—at a minimum—USPC indefinitely suspend its plans to implement the revisions to the Chapters. In the meantime. the Coalition welcomes the opportunity to continue to work with USPC in a joint and constructive effort to ensure that whatever changes to the Chapters USPC ultimately purports to make (i) accurately reflect scientific consensus; (ii) prioritize patient health and safety; and (iii) guarantee interested and affected parties the rights and process afforded to them by law.

* * * *

Sincerely,

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DLS

Enclosures

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Exhibit A

The shelf life of sterile medical devices

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Abstract

The issues of the shelf life of sterile medical devices and the concept of end-product sterility testing of a sample of devices to prove the sterility of a batch of sterile devices are discussed against the background of the probabilistic approach to sterility and sterilisation. The particular role that the sterilisation technique and the packaging materials used play in maintaining sterility are discussed against the background that sterility and the maintenance thereof is event- and not time-related, and the implications thereof on the shelf life of sterile medical devices.

Key words: sterile medical devices, sterility maintenance, shelf life

Introduction

Manufacturers of sterile medical devices often give an expiry ('use by') date on the package, generally five years from the date of sterilisation. The question arises as to what limits the duration of the sterility of such devices? Why is the shelf life limited by manufacturers, and if so, why specifically five years and not three or ten years – probably relating to the accelerated or real-time testing of the packaging material? This becomes particularly relevant in the case of medical implants such as prostheses. If the implant is specified by the manufacturer to have a shelf life of five years prior to implantation, how does this relate to the *in vivo* performance of the device? It should be clearly pointed out that in this discussion the emphasis is put on the sterility of the implant and not on the mechano-clinical performance of such a device.

In order to get perspective on this issue, it is necessary that we clearly understand the underlying principles of the particular sterilisation technique and the associated packaging of sterile medical devices.

The concepts of sterile, sterilisation and sterility assurance levels

In many authoritative books in the field of sterilisation, the concept sterile is referred to as a state completely free of any viable microorganisms, and sterilisation is defined as the process which will destroy all viable microorganisms.[1-3]

What limits the duration of the sterility of sterile medical devices?

These concepts are thus used in the *absolute* sense where no viable microorganisms exist.

However, an inherent problem is that it is *impossible in practice to prove either the complete absence or the destruction of these microorganisms*.[4] This will be discussed in more detail later.

The fact that the destruction of microorganisms through physical (radiation and steam) and chemical (ethylene oxide) sterilisation methods shows an *exponential dependence* on the various process parameters, clearly implies that the absence of microorganisms on a medical device following a properly validated sterilisation process can only be described in terms of a *probability function*.[4-5] This exponential nature of sterilisation means that, although the probability may reach a very low value, *it can never be lowered to a zero level in the absolute sense of the word*.[5-7]

This probabilistic approach to sterility leads to the concept of sterility levels – a view which no doubt may have little room in the 'classical' approach to sterility. Such a probabilistic approach also implies the existence of certain 'sterility assurance levels' (SALs) – a concept that plays an important role in this field and is being used to quantify the level or probability of sterility achieved through a certain sterilisation process.[8]

The SAL indicates the expected probability of finding a viable microorganism on a medical device after subjecting such a device to an acceptable and properly validated sterilisation process in which all process specifications are strictly adhered to, and is usually expressed as an exponential function – 10^{-n}.[6] The use of SALs improves the understanding of the efficacy of a sterilisation process and its practical significance.

Field of application as a determinant of the required Sterility Assurance Level (SAL)

The Association for the Advancement of Medical Instrumentation (AAMI) in the USA in the early seventies recognised that different SALs can be specified for medical devices, depending on the locality of their application.[9] In the ISO codes on sterilisation a similar distinction is made between two different medical device categories, depending on the intended field of application of such a device:

SAL 10^{-6}: surgically implanted devices
sterile fluid paths
other products transgressing natural tissue barriers;
implying that not more than one device in a *million* shall be non-sterile.

SAL 10^{-3}: topical products
mucosal devices
non-fluid path surfaces of sterile devices;
implying that not more than one device in a *thousand* shall be non-sterile.

With this approach, the contamination risk to the patient is the determining factor in selecting an SAL for a particular device. Those devices that are of an invasive nature will require a lower SAL than those that are non-invasive. Both categories will still be considered and classified as 'sterile' and appropriately labelled as such.

End-product sterility testing

The probabilistic approach to sterility and sterilisation has led to the concept and common practice of end-product sterility testing as proof of efficiency of a sterilisation process after completion. However, sterilisation is internationally recognised as an example of a process for which the efficacy cannot be verified by retrospective inspection and testing of the end product.[6] This implies that sterility testing of the end product cannot be applied to verify a SAL of smaller than about 10^{-2}, because the number of devices required as a representative sample for the sterility testing becomes both impractical and uneconomical. To perform end product sterility testing to uniquely 'prove' an SAL of 10^{-6} will require the sterility testing of one million devices. To further complicate matters, it is accepted that the inherent limitations of sterility testing typically leads to 'false positives' at a level of about 10^{-3}, which prevents end-product sterility testing to low SAL values.[10-11]

It clearly follows that end-product sterility testing of a few medical devices following sterilisation to 'demonstrate' or 'prove' that the entire batch is sterile, without a proper prior process validation, is without scientific foundation and can lead to erroneous conclusions with regard to the sterility of the batch as a whole.

However, it should be pointed out that the use of dosimeters (radiation) or biological indicators (steam and ethylene oxide) with a known accuracy and properly calibrated to monitor a properly validated sterilisation process, is completely acceptable and indeed essential, but they are employed to monitor the process parameters and not to prove the sterility of the resulting product.

The impact of sterilisation technique and packaging on the maintenance of sterility

Based on the basics of sterility and sterilisation, we return to our initial question on the shelf life of sterile medical devices – thus the maintenance of sterility prior to implantation. The sterilisation technique employed obviously plays a very important role on the nature and type of packaging that can be used.[12,13]

In the case of ethylene oxide gas sterilisation (EtO), the packaging material for both the primary and secondary packaging has to be selected to permit penetration by the sterilising gas to sterilise the devices, and its later removal at the end of the cycle. For this reason the polymer laminate packaging commonly used for radiation sterilisation cannot be used for gas sterilisation.

In the case of radiation sterilisation the device is hermetically sealed in double laminate pouches (polyethylene/polyester) – in general with a double seal and in the case of polymeric orthopaedic prostheses blanketed under ultra-pure nitrogen gas – the latter to protect the device or its polymeric components from radiation oxidative degradation during the radiation sterilisation cycle and subsequent storage. Radiation sterilisation has the advantage that the packaging integrity of these laminate pouches is particularly high and the author is not aware of any of such laminate pouches having failed during storage prior to use.

Radiation sterilisation has the advantage that the packaging integrity of these laminate pouches is particularly high

Sterility as a property of a medical device is recognised as event-related and not time-related

Provided a properly validated sterilisation process is used, and the integrity of the packaging is maintained, there is no reason to limit the shelf life of a sterile medical device – especially so in the case of radiation sterilisation. This clearly underlines the concept that sterility as a property of a medical device is recognised as event-related and not time-related. Should the packaging of a sterile medical device be compromised, it could lose its sterility directly after sterilisation. Similarly, if the packaging integrity is not compromised, the device will remain sterile.

The entire concept of the shelf life of medical devices is clearly still a topic that is hotly debated as follows from the international literature on the Internet, with the role of the packaging materials and the sterilisation techniques employed being the major points of discussion. Accelerated ageing of the packaging materials and seals that are generally used by manufacturers to set the shelf life are topics with their own inherent uncertainties.

No benefits of any form have been received from a commercial party related directly or indirectly to the subject of this article.

References

1. *Medical Microbiology,* Ed. R Cruickshank, p 680, E&S Livingstone Limited, London, 1968.
2. *Dorland's Illustrated Medical Dictionary,* 24th Edition, p 1440, WB Saunders Company, London, 1965.
3. Sykes G. *Disinfection and Sterilization,* Second Edition, p 6, E and F N Spon Limited, London, 1967.
4. Whitby JL. Resistance of microorganisms to radiation and experience with dose setting, in *Sterilization of Medical Products*, Volume 5, p 346, Polyscience Publications Inc., Canada, 1991.
5. Medical Devices – Validation and routine control of ethylene oxide sterilization, Draft International Standard ISO/DIS 11135, p 2, International Organization for Standardization, 1992.
6. Sterilization of Health Care Products – Methods for validation and routine control - Gamma and electron beam radiation sterilization. ISO/TC 198 WG 2 N16, pp 1 and 5, International Organization for Standardization, 1991.
7. Tallentire A, Khann AA. The sub process in defining the degree of sterility assurance, in *Sterilization by Ionizing Radiation,* Volume 2, pp 65 66, Multiscience Publications Limited, Montreal, 1978.
8. Ibid, p 5.
9. Masefield J, *et al.* A North American Viewpoint on Selection of Radiation Sterilization Dose, in *Sterilization by Ionizing Radiation,* Volume 2, pp 322-325, Multiscience Publications Limited, Montreal, 1978.
10. Sterilization of Health Care Products – Methods for validation and routine control - Gamma and electron beam radiation sterilization. ISO/TC 198 WG 2 N16, p 99, International Organization for Standardization, 1991.
11. ISO 11137-1: Sterilization of health care products – Radiation – Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices (2006).
12. ISO 11607-1: Packaging for terminally sterilized medical devices – Part 1: Requirements for materials, sterile barrier systems and packaging systems (2007).
13. ISO 11607-2: Packaging for terminally sterilized medical devices – Part 2: Validation requirements for forming, sealing and assembly processes (2007).

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Exhibit B

Journal of Pharmaceutical Sciences

A publication of the American Pharmaceutical Association

NOVEMBER 1969
VOLUME 58 NUMBER 11
Coden: JPMSA

Journal of Pharmaceutical Sciences

NOVEMBER 1969
VOLUME 58 NUMBER 11

REVIEW ARTICLE

The Sterility Testing of Pharmaceuticals

FRANCES WILLARD BOWMAN

Keyphrases ☐ Sterility testing—pharmaceuticals ☐ Sampling procedures—sterility testing ☐ Culture media—sterility testing ☐ Incubation time, temperature—microorganism detection ☐ Indicators, biological—sterility testing ☐ Environmental conditions—sterility testing ☐ Methods, sterility testing—pharmaceuticals

The administration of drugs by parenteral routes has required the development of meaningful sterility tests to be used in the analytical control of these pharmaceuticals. Proom (1) postulated that sterility tests should either demonstrate the absence of microorganisms or provide an estimate of the actual numbers and types of organisms present. The latter data are intended to show that there are insufficient numbers or types of organisms to be dangerous to the consumer or to actually degrade the product. Sterility tests appeared in the *British Pharmacopoeia* for the first time in 1932; before then the Regulations issued under their Therapeutic Substances Act of 1925 specified sterility tests for certain vaccines, toxins, serums, and similar products as well as for insulin and arsphenamine (2). Sterility tests were first introduced into the *United States Pharmacopeia* when USP XI became official on June 1, 1936. In the same year, the Sixth Edition of the *National Formulary* (*NF*) also included a sterility test for ampul solutions.

Both the USP and the NF are recognized as official compendia by the Federal Food Drug, and Cosmetic Act and by comparable laws of the individual states of the United States. The Congress recognized these compendia as sources of standards for strength, quality, and purity of drugs moving in interstate commerce. Since the first sterility tests were introduced, the compendia have been active in fostering new procedures and adopting changes that have increased the sensitivity of the tests.

In addition to the official compendia, two Federal agencies promulgate regulations governing the sterility testing of pharmaceuticals. At the turn of the century the first federal legislation was enacted to provide for the production of vaccines under government license. Under this law, the Hygienic Laboratory of the Public Health Service was created. As the list of vaccines grew and was augmented by serums, toxins, antitoxins, and blood products, the agency responsible for supervising production and establishing the purity and potency standards for them also grew (3). The sterility tests for these products, known as "biologics," are described in Public Health Service Regulations, which issue from the Division of Biologics Standards of the National Institutes of Health, Bethesda, Maryland, Title 42, part 73.73 (4). In 1945 Congress gave the Food and Drug Administration (FDA) authority to set standards for antibiotics. This authority included the testing and certification of each batch prior to distribution. For the purpose of administering the certification program, standards of potency and purity of antibotics are established under Title 21 of the Code of Federal Regulations and are published in the *Federal Register* (5). They include a sterility test procedure for each antibiotic required to be sterile. For both biologics and antibiotics, the compendial monographs conform to the appropriate regulations of the regulatory agency. Both agencies have contributed to advances in sterility test methodology, and members of their staffs have cooperated with the revisers of the compendia in performing investigational studies on procedures, media, temperatures, and time of incubation.

The first sterility test described in the compendia was applied only to sterile liquids. Only one medium, a beef-

peptone broth, was used. Half the tubes of this medium were inoculated with 5 drops (0.2 ml.) of the liquid; the other half with 20 drops (0.8 ml.). After the inoculated tubes were incubated for 7 days at 37°, they were examined for the presence or absence of microbial growth. When USP XII became official in 1942, it provided for a test to detect aerobic as well as anaerobic microorganisms in sterile solids and liquids and also included procedures for the inactivation of certain preservatives.

USP XIII introduced the use of a clear broth medium, fluid thioglycollate, for the cultivation of aerobic, microaerophilic, and anaerobic bacteria, and a honey medium for the recovery of molds and yeasts. Tests of samples in fluid thioglycollate medium were incubated for 7 days at 37°, whereas cultures of material in honey medium were incubated for 15 days at 22–25°. USP XIII also included for the first time a brief description of the laboratory area to be used for performing sterility tests. It stressed the importance of having qualified personnel, trained in aseptic techniques, to perform the tests.

In USP XIV (1950) the incubation temperature for thioglycollate was lowered from 37° to 32–35° and Sabouraud Liquid Medium (modified) containing a peptone and dextrose replaced the honey medium for molds and yeasts. In USP XV fluid thioglycollate was still the medium for bacteria, but Sabouraud Liquid Medium (modified) was changed to USP Fluid Sabouraud Medium, which specified the use of two peptones (pancreatic digest of casein and peptic digest of animal tissue) and dextrose.

The sterility tests described in USP XVI and XVII remained essentially the same as in USP XV; however, according to the galley proof of the chapter on Sterility Testing, major changes are expected in the forthcoming USP XVIII. The sterility tests in the *National Formulary* have generally been comparable to those of the USP. Therefore, it is anticipated that NF XIII, which will be published in 1970, –or a Supplement to NF XIII– will also include similar modifications.

The history of the sterility tests in the USP and NF since 1936 shows that official methods are constantly changing. The changes, which are also common to official compendia of other countries, reflect improved techniques, procedures, and media for detecting microorganisms from any item or medicament required to be sterile.

PRINCIPLES OF STERILITY TESTING

The general principles governing the design and interpretation of sterility tests were expounded by Bryce (6). He elaborated on the limitations of the methods of testing described by various official compendia. These limitations derive from two practically insoluble problems. The first is that of adequate sampling, and the second is the inability to cultivate all viable microorganisms that may be present. He stated that pharmacopeias imply that sterility is the state of being free from living organisms of all types. This concept is simple enough, but unfortunately it is unreal, being incapable of experimental verification. Bryce concluded that the sterility test is, in fact, a test for only certain contaminant organisms. In addition, he said that since the test attempts to infer the state of the whole from the result of an examination of the part, it is essentially a statistical operation. The forthcoming USP XVIII will recognize the difficulties of the experimental verification of the sterile state. Therefore, it will probably explain the objectives of the sterility test as well as the limitations. It is likely to be expressed as follows: The objective of the sterilization process is to make the article safe for use, but the sterility tests may be expected to reveal only that living organisms have been removed or destroyed to the extent that they no longer multiply in appropriate culture media under favorable conditions. Interpretation of the results of sterility tests must allow for the possibility that the degree of contamination is of a low order of magnitude. Confidence in the results of the tests with respect to a given lot of articles is based upon knowledge that the lot has been subjected to a sterilization procedure of proven effectiveness. Sykes (2) pointed out that it is clearly a prerequisite that before a preparation is submitted to a test for sterility, it must have been subjected to such a treatment as can be reliably expected to yield a sterile product. The exclusive purpose of the test is to check that the approved sterilization process has been carried out satisfactorily; the test cannot of itself check that the process is satisfactory.

SAMPLING PROCEDURES

The proper sample size and sampling procedure for the sterility test has been the subject of much debate and discussion among manufacturers and control authorities of parenteral drugs. The relative merits of sampling schemes based on constant sample size, regardless of lot size, versus those based on proportional samples, were reviewed by Bryce (6). The statistical properties of sampling plans have been dealt with by Knudsen (7), by Greenberg (8), and by Brewer (9). Knudsen demonstrated that the probability of accepting lots having a given percentage of contaminated containers is directly related to sample size rather than batch size. Brewer considered the problems associated with sampling for sterility testing and pointed out the mathematical limitations of the procedures. The relationships of the probabilities of acceptance of batches of varying assumed degrees of contamination to sample size were tabulated. Probability values for eight sample sizes were given. Greenberg stated that from a controller's viewpoint it is essential that sterility tests be performed, but he made it clear that regardless of the size of the sample and the techniques used, the tests would detect only grossly contaminated lots. To compensate for this, he advocated that pharmaceutical and biological manufacturing be strictly controlled.

The difficulty of establishing procedures that would be accepted internationally is evident in the WHO Report of General Requirements for the Sterility of Biological Substances (10). The WHO Study Group considered various rules for sampling finished containers which had been proposed or adopted in different countries. The Study Group agreed that it was not possible to decide which of these rules for sampling should be preferred and that the Requirements should

permit the adoption of any rule, based on the principles of sampling statistics, found to be satisfactory by the national control authorities of individual countries. For sampling among final containers, one of its members (10) proposed the testing of a sample equal to four-tenths of the square root of the number of articles in the batch. Mathews (11) cast doubt on the validity of this proposal, since it appeared that the best control would be achieved (in batches contaminated 2–4%) when the sample size was proportional to the number of articles in the batch. However, he agreed with Knudsen (7) that proportional sampling would lead to very poor control over small batches and would be impracticable for extremely large batches due to overwhelming interference by accidental contaminations. Proom (12) showed that the size of the sample is not limited in practice by statistical consideration of the risk of accepting contaminated batches. The size of the sample is limited by empirical considerations of the risk of rejecting sterile batches because of accidental contamination during the testing process. Another report (13) stated that it is difficult to fix a value for a certain fixed risk (r) of extraneous contamination during the sterility test. However, a value of 1% for r was regarded as a reasonable possibility.

At the London Round Table Conference on Sterility Testing in 1963 (14) the participants concluded that the control authority should satisfy itself that the manufacturer has taken all necessary precautions to ensure the production of a sterile product, since sterility tests employing reasonable sampling detect only gross contamination. They recognized that the lowest contamination rates which can be detected with at least 95% probability are 28, 15, and 7% when testing 10, 20, and 40 samples, respectively, and that accidental contamination will weaken the test further. Most of the speakers wanted the number of final containers tested to be independent of the batch size. The majority concluded that experience of manufacturing laboratories showed that testing between 10 and 20 vials from a final lot has regularly given no untoward reactions associated with lack of sterility. Therefore, this number of vials was regarded as sufficient for the test on a final lot.

The USP and NF require a representative sample of 10 units to be examined from products sterilized by steam under pressure, and a representative sample of 20 units for all other products. The *Public Health Service Regulations* require 20 final containers from each filling of each lot, selected to represent all stages of filling from the bulk container. The *Antibiotic Regulations* require 20 immediate containers collected at approximately equal intervals from each filling operation. A filling operation is defined as that period of time not longer than 24 consecutive hours during which a homogeneous quantity of a drug is being filled continuously into market-size containers and during which no changes are made in equipment used for filling.

CULTURE MEDIA

From the time of the first sterility tests until the present, the test results have been influenced by the types and sensitivity of the culture media. Since no single medium will support the growth of all bacteria, molds, and yeasts, more than one medium must be used. The question of which to use has been the subject of many conferences, study groups, and published reports. However, Pittman (15) concluded that none of these have supplied adequate support for the selection of any medium in preference to others in use in various control laboratories. She pointed out a possible shortcoming of published work in that the growth-promoting properties of various media were determined by using microorganisms considered to be potential contaminants, rather than by using organisms actually isolated from contaminated products. She advocated that emphasis be given to the recovery of organisms subjected to insult by preservatives.

Many media are being used for sterility testing, and the formulas for these appear in the pharmacopeias of many countries. In the report of a WHO Study Group (10) formulas were listed for nine media for culturing bacteria and six for culturing fungi. The Group could not recommend any one medium in preference to another because of lack of comparative data.

In 1949 Brewer (16) introduced the use of sodium thioglycollate to provide aerobic and anaerobic conditions in one medium. After extensive studies of the medium for the sterility test, Pittman (17) agreed that it provided both aerobic and anaerobic conditions in one test tube. In addition, it neutralized the bacteriostatic action of mercurial preservatives. Sabouraud liquid medium has been widely used for the detection of fungi since 1950. Since the advent of these media, few changes have been made.

Benković and Higy-Mandić (18) presented comparative studies of the growth of yeasts and bacteria in various common media. Although fluid thioglycollate had become firmly established by 1956 for the cultivation of both anaerobic and aerobic bacteria some investigators preferred the use of sodium hydrosulfite suggested by Bonnel (19) as an oxidation-reduction potential regulator. Jeskova (20) found that of five media tested against 272 strains of 20 species, fluid thioglycollate and the Clausen modified hydrosulfite media gave the best results. Mathews (11) reviewed the controversy centered around the use of sodium hydrosulfite as an oxidation-reduction potential regulator in lieu of thioglycollate. The hydrosulfite medium, the thioglycollate medium, and a corn steep liquor with both thioglycollate and hydrosulfite were discussed. Mossel and Beerens (21) studied the inhibitory properties of four different types of thioglycollate media. Using wet spores of fourteen strains of *Clostridium*, he found sodium thioglycollate to be toxic *per se* to almost all strains tested. The degree of toxicity was influenced by other components of the medium. He recommended that cysteine hydrochloride be used as the redox potential reducing compound instead of sodium thioglycollate.

Chauhan and Walters (22) used common air-borne saprophytic fungi to demonstrate that the *British Pharmacopoeia* test for sterility was unable to recover fungal contamination. The inclusion of a specific test for fungi comparable to that described in the USP was recommended for the BP

Two recent papers (23, 24) present data to show that thioglycollate medium does not support growth of

Bacillus subtilis spores when they are entrapped or held so that the organisms cannot be released into an environment of high oxygen tension.

Although liquid Sabouraud medium has been used successfully to recover molds and yeasts from small inocula, many investigators oppose the use of a selective medium in sterility testing. Since the purpose of performing the test is to detect as many microorganisms as possible, it is undesirable to use a medium such as fluid Sabouraud that was designed to inhibit certain bacteria. For this reason, it is believed that the 18th revision of the USP will replace Sabouraud medium with a soybean-casein digest medium which has been shown to support the growth of many bacteria as well as fungi.

TIME AND TEMPERATURE OF INCUBATION

Originally the sterility test medium was incubated at 37° for pathogenic bacteria, and at about 25° for psychrophilic bacteria and fungi. Since common airborne saprophytic bacteria represent a greater potential source of contamination of pharmaceutical products than the more fastidious pathogens, in 1950 the compendia reduced the temperature of incubation from 37° to 32–35°. The stimulus for the 1955 change to 30–32° for fluid thioglycollate was brought about by a dramatic incident (15). The Division of Biologics Standards of the National Institutes of Health discovered a failure to detect the presence of a pseudomonad contaminant in plasma. The contaminated plasma caused severe shock when administered to patients. It was later discovered that the contaminant grew at room temperature but was killed at 35°. As a result of this finding, in 1955 the temperature for the incubation of fluid thioglycollate was lowered from 32–35° to 30–32° in the Federal Regulations and in the official compendia.

Pittman and Feeley (25) showed that although the yeasts and fungi they studied were cultivated easily at 22° (compared with other temperatures within the range of 4–35°), the number of strains recovered in fluid thioglycollate medium incubated first at 22° for 3 days and then at 30° for seven days was only slightly less than in the best combination of medium and temperature.

Mathews (11) has reported that the method of incubating first at a low temperature and then at a higher one has been used in some laboratories for years. He also postulates that it is plausible that starting incubation in any medium at a low temperature may encourage elution, from the surface of any microorganism present, of any antiseptic which might be adsorbed. Thus, the preliminary low temperature incubation would mitigate the harmful effect to be expected if the organism were to be exposed to the action of adsorbed antiseptic at a higher temperature.

The use of a single medium, thioglycollate, incubated for 3 days at 21 ± 1° and 7 days at 31 ± 1° for the sterility testing of antibiotics was explored and rejected (26). Brewer and Keller (27) presented data which support the existence of slow-growing organisms that could not be detected until the 21st day of incubation. These findings are in keeping with those of other workers who have pointed out the slow growth of organisms subjected to less than the lethal radiation dosages.

The 18th revision of the USP will likely require no less than 14 days of incubation for fluid thioglycollate and for soybean-casein digest broth, except for preparations tested by membrane filtration. The incubation time for preparations tested by filtration sterility test will probably be no less than 7 days. The fluid thioglycollate will be incubated at 30–35° and the soybean-casein digest medium will be incubated at 20–25° for pharmaceutical preparations tested by either of the two prescribed sterility tests. If the nature of the product or the sterilization procedure used is conducive to producing the "slow-grower" phenomenon, additional incubation time for these preparations may be required.

BIOLOGICAL INDICATORS

In recent years biological indicators have been employed in addition to sterility tests to demonstrate the adequacy of some sterilization procedures. A single species of viable microorganisms of known resistance to the sterilization process being employed may be added directly to representative units of the batch being sterilized. If this is not feasible, the culture is added to disks or strips of paper or metal, or glass beads which are incorporated in or on the product. The biological indicator (BI) is removed after the sterilization cycle, transferred to culture media, and incubated at the appropriate temperature to determine whether the microorganisms of the BI have been destroyed. The effective use of BI's for monitoring a sterilization process requires a knowledge of the product being studied and of the probable types and numbers of the microbial population in the product prior to sterilization. Brewer and Phillips (28), in a paper which elaborates on the proper use of BI's, discussed the selection of the indicator to be used with various sterilization procedures, the preparation and calibration of the indicator carrier system, and the placement of the BI in the sterilization system. Bruch (29) emphasized that BI's should not be used as biological thermocouples. They are not suited to measuring physical processes which can be monitored by other types of indicators. For example, if the measurement of time and temperature is a necessary part of the sterilization cycle, it is better to use physical monitoring techniques. The BI's should be employed to demonstrate that the cycle used is capable of killing the largest population of resistant organisms that can be expected to contaminate any batch of the product to be sterilized. Bruch believes that the use of BI's is a necessary adjunct to gaseous and radiation sterilization since all the variables in the process cannot be properly monitored by physical instrumentation.

A variety of microorganisms have been used for BI's to verify the sterilization procedures used for pharmaceuticals. Spores of *Bacillus subtilis* var. *niger* are widely used as a wet and dry heat sterilization control. *Bacillus pumilus* is used in Europe and America for radiation sterilization control. Christensen *et al.* (30) has suggested *Streptococcus faecium* as a BI for radiation sterilization, but warned that the radiation resistance of any microbiological species shows great differences in resistance between various strains of the same species. The use of *Bacillus stearothermophilus* spores has been approved by the National Institutes of Health as a sterilizer control

for use in licensed establishments which produce biologicals. This organism meets the rigid requirements of the PHS *Regulations*, Title 42, Part 73 (4) because it does not produce pyrogens or toxins, is not pathogenic for man, and does not grow at or below 37° within a 2-week period. In addition, these Regulations give detailed instructions concerning the handling of microbial spores and prohibit their transfer to culture media in areas used for manufacture of products.

In the last few years manufacturers of pharmaceuticals have found that BI's, in addition to sterility tests, are of great value in establishing and monitoring their sterilization procedures. Due to the increased acceptance, a number of biological spore indicators are commercially available.

In order to give official recognition to the use of BI's as meaningful adjuncts to the sterility tests, it is expected that the XVIII revision of the USP will include guidelines for their proper use.

ENVIRONMENTAL CONDITIONS

It is axiomatic that if the results of sterility tests are to be reliable, they must be performed in a sterile environment. For this reason Federal Regulations and the compendia state that the tests should be performed in an area as free from microbial contamination as is possible to achieve. It is anticipated that the chapter on Sterility Tests for USP XVIII will state that ideally, the sterility test area should comply with Class 100 conditions as described in Federal Standard No. 209A, entitled "Clean Room and Work Station Requirements, Controlled Environment," and NASA Standard for "Clean Rooms and Work Stations for Microbially Controlled Environment," as described in NHB5340.2, Aug. 1967.

For many years sterility tests were performed in conventional clean rooms, equipped with germicidal lamps and filtered air under positive pressure. All surfaces of the rooms were washed daily with germicides. Personnel who performed the tests donned sterile gowns, caps, masks, shoes, and gloves. Nevertheless it was apparent that all these precautions were inadequate. Airborne microbial contamination was a constant problem which could cause false-positive results. One difficulty was that employees working in these areas were constantly shedding particles containing microorganisms (31). Whitfield (32), working for the aerospace industry, was assigned to study and improve the conventional clean rooms which were then in use. He noted that in the conventional clean room the filtered air, which is forced through wall or ceiling ducts, creates swirls and eddies in the airstream which, in turn, trap particles and microorganisms within the room. From this observation there evolved in 1961 the concept of laminar air flow—a bank of filtered air moving through a work area at just the proper speed to sweep contamination with it and to create a minimum of turbulence and a minimum effect on workers. Laminar flow is defined by Federal Standard 209a as "air flow in which the entire body of air within a confined area moves with uniform velocity along parallel lines, with a minimum of eddies" (33). Brewer (34) reported on the use of laminar flow hoods in sterility testing. He concluded from his experience that the use of laminar flow equipment affords a practical means for conducting sterility tests. In addition, he stated that conducting valid tests on items such as tubing and gloves without the use of such equipment would be an almost insurmountable task. A review paper on laminar air flow by Davies and Lamy (35) described the advantages of laminar air flow over conventional clean rooms and suggested its use in hospital pharmacies and wards. Manning (36) presented interesting results of microbial studies in a laminar air flow unit used for sterility testing. Over 200 tests were performed in this unit without a contamination problem. One publication (37) described the successful use of a laminar flow unit to aseptically fill and close 460 syringes. Parisi and Borick (38) performed mock sterility tests in a laminar flow sterile room and in a conventional sterile room. The tests employed all of the necessary testing motions with the exception of placing a sample into the medium. The tests performed in the laminar flow sterile room yielded 0.5% positives whereas 1.5% positives were obtained in the conventional sterile room. He concluded that laminar flow is significantly better for providing a microbiologically clean area for sterility testing procedures than a conventional sterile room with filtered air. Bowman (39) evaluated the use of vertical laminar flow hoods for the sterility testing of antibiotics and insulin. An aerosol study employing the tracer organism, *Serratia marcescens*, proved the ability of these hoods to remove airborne contamination. Three 1.8-m. (6-ft.) vertical laminar flow hoods installed in clean rooms (see Fig. 1) have been used satisfactorily for approximately 2 years for performing sterility tests on antibiotic and insulin preparations. The air entering each clean room is filtered through HEPA[1] filters located in the ceiling. There is an air change in each room every three minutes.

In order to obtain quantitative information on the control of the air in clean rooms, laminar flow rooms, and the work areas of the laminar flow hood, a variety of volumetric samplers have been designed and evaluated. After six years of fundamental research, Luckiesh *et al.* (40) developed two highly efficient electrostatic air samplers. Kuehne and Decker (41) conducted studies on several factors affecting the efficiency of air sampling when vegetative cells of microorganisms were collected for extended periods of time. He found that slit samplers afford a time-concentration relationship, permit air sampling for longer periods of time at a good collection efficiency, and require a minimum of labor, personnel, and equipment to take the samples. *Public Health Monograph* No. 60 (42) gives an excellent discussion of commercially available instruments for sampling airborne bacteria. It also describes techniques for numerical determination of the microflora of air.

METHODS FOR STERILITY TESTING

There are two basic recognized methods for performing sterility tests of pharmaceuticals. One is the direct method, which allows the test sample to be inoculated directly into the appropriate culture medium. The other is the bacterial membrane filter method, in which the sample is solubilized in a non-toxic diluting fluid which

[1] High Efficiency Particulate Air Filters.

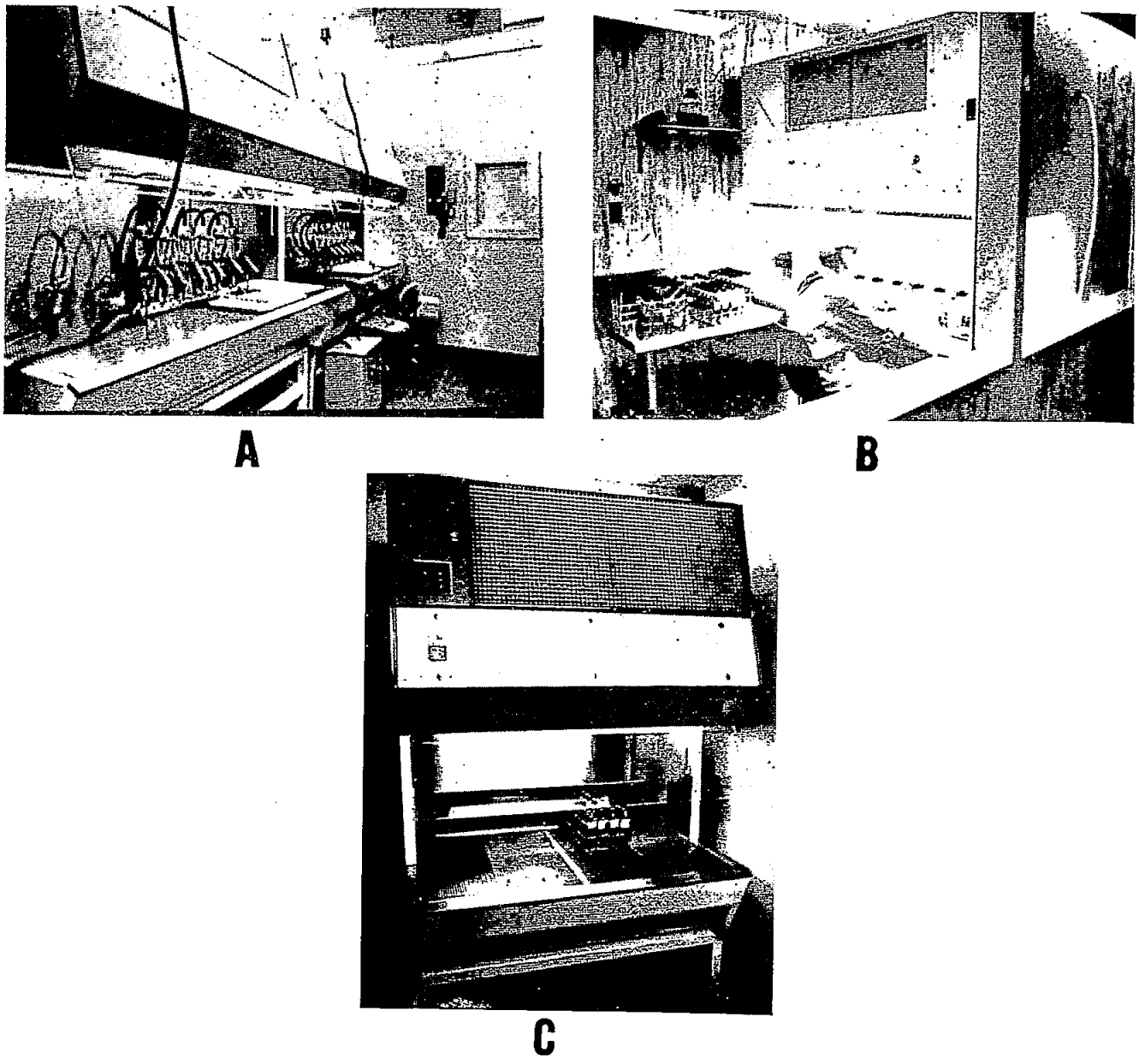

Figure 1—*Laminar air flow hoods used in the sterility testing of antibiotics and insulin.* A, *Two 1.8-m. (6-ft.) vertical laminar flow hoods;* B, *One 1.8-m. (6-ft.) vertical laminar flow hood;* C. *One 1.2-m. (4-ft.) vertical laminar flow hood used for aseptically transferring sterile enzymes to sterile broth. Reprinted from* Bull. Parenteral Drug Assoc., *22, 57(1968).*

is then filtered through a bacterial-retentive membrane usually composed of cellulose esters. The membrane is washed to remove any inhibitory substances contained in the sample, and is then transferred aseptically to an appropriate medium. This filtration method was first introduced by Holdowsky (43) to separate microorganisms from the antimicrobial effects of antibiotics in order to obtain reliable sterility tests of antibiotic drugs. Research on the application of the membrane filtration technique to the sterility testing of antibiotic drugs by Bowman (44) produced practical methods for solubilizing and filtering a number of antibiotic preparations. The *Antibiotic Regulations* (45) were amended in 1964 to incorporate the filtration procedures, which greatly increased the sensitivity of the antibiotic sterility tests. The direct type of sterility test formerly used, when applied to all antibiotics except penicillin, detected only those organisms highly resistant to the inhibitory action of the particular antibiotic. In the case of penicillin, the enzyme penicillinase was added to the medium to inactivate the antibiotic.

Several reports (46–52) confirmed the soundness of the membrane filtration approach for sterility testing of antibacterial substances. The filtration techniques have also been successfully applied to testing the sterility of oils and ointments (53–55).

The 1963 *British Pharmacopoeia* introduced the membrane filtration test and required its use for antibiotics other than penicillin. It is anticipated that the eighteenth revision of the USP will allow a filtration sterility test which will be especially valuable for products that contain bacteriostatic or fungistatic preservatives. Alternatively, these products may be tested by the direct method provided these substances are diluted beyond an

inhibitory level. The details of the performance of the sterility test are given in all official compendia and Federal Regulations. They include the media to be used, the time and temperature of incubation, and directions on how to interpret the test results. All regulations governing sterility testing allow for the contingency of accidental contamination introduced in the performance of the test, and therefore provide for one or more retests.

Whatever testing system is employed, it is essential that the technique be continuously and adequately controlled. The USP and NF require that control tubes of each medium be incubated at the time of the test to assure sterility of the entire batch of medium. They further require that each lot of medium be tested for its growth-promoting qualities, using two or more strains of microorganisms that are exacting in their nutritive requirements. Sykes (56) presented an excellent review of the information made available by the Standardization Subcommittee of the Society for General Microbiology on methods of manufacturing bacterial culture media. Farber and Seligmann (57) recommended the use of small inocula of *Bacteroidis vulgatus* ATCC 8482 to test the anaerobic growth-promoting qualities of fluid thioglycollate medium.

DISCUSSION

The state of the art of sterility testing is changing rapidly and such changes are reflected in revisions and amendments to official requirements for sterility tests. There is still controversy over whether it is better to test for the efficiency of the sterilization process or to test the sterilized product. Most control authorities insist that the sterilization process be proven and that the sterile products also be tested. Our objective is to seek the maximum information from a balanced amount of testing, and to provide pharmaceuticals that are free from microbial contamination.

REFERENCES

(1) H. Proom, *Proc. Round Table Conf. Sterility Testing, London, 1963*, A17.

(2) G. Sykes, *J. Pharm. Pharmacol.*, **8**, 573(1956).

(3) L. C. Miller, *Am. J. Pharm.*, **138**, 175(1966).

(4) *Code of Federal Regulations*, Title 42, Part 73 (revised as of January 1, 1969).

(5) *Ibid.*, Title 21, Parts 130 to end (revised as of January 1, 1969).

(6) D. M. Bryce, *J. Pharm. Pharmacol.*, **8**, 561(1956).

(7) L. F. Knudsen, *J. Am. Pharm. Assoc., Sci. Ed.*, **38**, 332 (1949).

(8) L. Greenberg, *Proc. Round Table Conf. Sterility Testing, London, 1963*, B1.

(9) J. H. Brewer, in "Antiseptics, Disinfectants, Fungicides, and Sterilization," 2nd ed., G. L. Reddish, Ed., Lea & Febiger, Philadelphia, Pa., 1957, p. 160.

(10) World Health Organization Technical Report Series No. 200, "Requirements for Biological Substances. 6. General Requirements for the Sterility of Biological Substances," World Health Organization, Geneva, 1960.

(11) A. G. Mathews, *Australasian J. Pharm.*, **44**, S 62 (1963).

(12) H. Proom, *Proc. Intern. Congr. Microbiol. Standardization, 7th*, E. & S. Livingstone Ltd., Edinburgh and London, 1962.

(13) M. W. Bentzon, "Note on Sampling for Sterility Control," unpublished working document WHO/BS/IR/75, World Health Organization, Geneva, 17 April 1959, p. 4.

(14) *Proc. Round Table Conf. Sterility Testing, London, 1963*, B31.

(15) M. Pittman, *ibid.*, C6.

(16) J. H. Brewer, *J. Bacteriol.*, **39**, 19(1940).

(17) M. Pittman, *ibid.*, **51**, 19(1946).

(18) J. Benković and L. J. Higy-Mandić, *Proc. Intern. Meeting Biol. Standardization 3rd, Opatija*, **1957**, 373.

(19) P. H. Bonnel, *Ann. Inst. Pasteur*, **79**, 422(1950).

(20) Z. Jeskova, *Appl. Microbiol.*, **8**, 274(1960).

(21) D. A. A. Mossel and H. Beerens, *J. Hyg.*, **66**, 269(1968).

(22) N. M. Chauhan and V. Walters, *J. Pharm. Pharmacol.*, **16**, 46T(1964).

(23) J. E. Doyle, W. H. Mehrhof, and R. R. Ernst, *Appl. Microbiol.*, **16**, 42(1968).

(24) F. W. Bowman, "Culture Media for Sterility Tests of Antibiotics," manuscript in preparation.

(25) M. Pittman and J. C. Feeley, *Proc. 7th Intern. Congr. Microbiol. Standardization, 7th*, E. & S. Livingstone Ltd., Edinburgh and London, 1962.

(26) F. W. Bowman, *Bull. Parenteral Drug Assoc.*, **16**, No. 6, Nov.-Dec. p. 15 (1962).

(27) J. H. Brewer and G. H. Keller, in "Radiosterilization of Medical Products," International Atomic Energy Agency, Vienna, 1967, p. 311.

(28) J. H. Brewer and G. B. Phillips, *Bull. Parenteral Drug. Assoc.*, **22**, 157(1968).

(29) C. W. Bruch, *Conf. Disposable Sterile Med. Prod.*, Washington, D. C., 1967.

(30) E. A. Christensen, N. W. Holm, and F. A. Juul, in "Radiosterilization of Medical Products," International Atomic Energy Agency, Vienna, 1967, p. 265.

(31) G. W. Sciple, D. K. Riemensnider, and C. A. J. Schleyer, *Appl. Microbiol.*, **15**, 1388 (1967).

(32) W. Whitfield, *Contamination Control*, **3**, 16(1964).

(33) Federal Standard No. 209, Clean Room and Work Station Requirements, Controlled Environment, General Services Administration, Business Service Center, Washington, D. C., December 16, 1963.

(34) J. H. Brewer, Round Table on Sterility Testing, Annual Convention of the American Society for Microbiology, Los Angeles, Calif., 1966.

(35) W. L. Davies and Peter P. Lamy, *Hospital Pharm.*, **3**, 7 (1968).

(36) J. E. Manning, "Microbial Studies in the Laminar Air Flow Room," presented at the Annual Convention of the American Association for Contamination Control, Houston, Texas, 1966.

(37) P. P. Lamy, W. L. Davies, R. DiStefano, and M. E. Kitler, *Drug Intelligence*, **2**, 213(1968).

(38) A. N. Parisi and P. M. Borick, "The Application of Laminar Flow to Sterility Testing," presented at the Annual Convention of the American Association for Contamination Control, Chicago, Ill., 1968.

(39) F. W. Bowman, *Bull. Parenteral Drug. Assoc.*, **22**, 57(1968).

(40) M. Luckiesh, A. H. Taylor, and L. L. Holladay, *J. Bacteriol.*, **52**, 55(1946).

(41) R. W. Kuehne and H. M. Decker, *Appl. Microbiol.*, **5**, 321 (1957).

(42) H. W. Wolf, P. Skaliy, L. B. Hall, M. M. Harris, H. M. Decker, L. M. Buchanan, and C. M. Dahlgren, "Sampling Microbiological Aerosols," *Public Health Monograph* No. 60, April 1959.

(43) S. Holdowsky, *Antibiot. Chemotherapy*, **2**, 49(1957).

(44) F. W. Bowman, *J. Pharm. Sci.*, **55**, 818(1966).

(45) *Code of Federal Regulations*, Title 21, Section 141.2, *Federal Register*, **29**, 4119(1964).

(46) M. Gay, *Pharm. Acta Helv.*, **35**, 555(1960).

(47) H. Lagodsky, *Compt. Rend. Soc. Biol.*, **154**, 1435(1960).

(48) S. Lambin, F. Sebastien, and J. Bernard, *Ann. Pharm. Franc.*, **20**, 749(1962).

(49) J. W. Lightbown, *Proc. Round Table Conf. Sterility Testing, London, 1963*, E6.

(50) H. A. Frediani, *Bull. Parenteral Drug. Assoc.*, **18**, 25(1964).

(51) M. Gay and B. Fust, *Zentr. Bakteriol. Parasitenk.*, **197**, 389(1965).

(52) E. Cuboni, *Boll. Int. Sieroterap. Milan.*, **41**, 63(1962).

(53) R. Russomanno and E. G. Wollish, *J. Pharm. Sci.*, **53**, 1538(1964).

(54) M. White, F. W. Bowman, and A. Kirshbaum, *ibid.*, **57**, 1061(1968).

(55) F. W. Bowman, *J. Pharm. Sci.*, in press.
(56) "Constituents of Bacteriological Culture Media," G. Sykes (Ed.), Society for General Microbiology, Cambridge University Press, England, 1956.
(57) J. F. Farber and E. B. Seligmann, Jr., *Appl. Microbiol.*, **16**, 1102(1968).

ACKNOWLEDGMENTS AND ADDRESSES

Received from the *Division of Pharmaceutical Sciences, National Center for Antibiotics and Insulin Analysis, Food and Drug Administration, Department of Health, Education, and Welfare, Washington, DC 20204*

RESEARCH ARTICLES

Surface Pressure Relaxation and Hysteresis in Stearic Acid Monolayers at the Air-Water Interface

JAMES W. MUNDEN, DAVID W. BLOIS, and JAMES SWARBRICK*

Abstract ☐ Time-dependent changes in the surface pressure of stearic acid monolayers were examined using an automated Wilhelmy-type film balance. Different surface pressure-area isotherms were obtained for two different rates of compression. Pressure relaxation from preselected surface pressures was examined as a function of time. The results indicated two types of relaxation which, along with the compression rate effect, may be rationalized on the basis of changes in molecular orientation and redistribution, together with expulsion from the monolayer at areas below the limiting area per molecule. Marked hysteresis effects were also noted when stearic acid monolayers were subjected to compression-expansion cycles. The effect of repeated cycling and the minimum area of compression on hysteresis were investigated. The onset and extent of hysteresis may also be explained on the basis of expulsion and reentry and orientation and redistribution of molecules at the interface.

Keyphrases ☐ Stearic acid monomolecular films—effect of compression rate ☐ Surface pressure relaxation—stearic acid monolayers ☐ Hysteresis—effect of minimum area of compression ☐ Cycling, requested, effect—hysteresis ☐ Air-water interface—Surface pressure

In recent years, the study of monomolecular films of biologic materials spread at the air-liquid interface has become increasingly significant in pharmaceutical and medical research. Serving as simulated biologic interfaces, these systems have been used to examine the interactions of such medicinal agents as the phenothiazines, local anesthetics, bactericides, and antibiotics with various cell membrane constituents. The evaluation of such studies is based primarily on the surface pressure-area per molecule (π-A) relationships exhibited by the system and the manner in which these change with time.

There are many factors affecting the shape and type of surface pressure-area diagram obtained for monolayers. Influencing factors such as pH, temperature, and the ion content of the supporting media have received fairly extensive investigation and are well documented in several texts (1–4). The time-dependency of surface pressure has been examined under conditions of slow discontinuous compression (5–7) and more rapid continuous compression (8–11). With the exception of the work of Rabinovitch *et al.* (11), the treatment of the time effects in these papers is limited. Examination of the literature shows that monomolecular film studies have been undertaken using a wide range of compression rates and methods of compression. This arises, presumably, from the lack of appreciation of the time-dependent properties of monomolecular films. Accordingly, investigations were undertaken to examine the effects of compression rate on the surface pressure-area isotherms of stearic acid monolayers and to study surface pressure relaxation, *i.e.*, the decrease in surface pressure with time when compression is stopped and the film held at constant area.

The property of surface hysteresis was also examined since it appeared there might be a link between the time-dependency of surface pressure and this property. Surface hysteresis or the significant separation seen between compression and expansion surface pressure-area isotherms has been examined in the case of the biological surfactants obtained from lung tissue, the so-called pulmonary or lung surfactants (12–15); however, the ability of simpler compounds such as stearic acid to exhibit similar behavior has been almost ignored. Ries and Walker (16) have stated, without presenting any evidence, that compression-expansion isotherms for stearic acid show hysteresis.

As a result of studies on the monolayer properties of biologic amphiphiles currently under investigation in this laboratory, the authors wish to report their observations on (*a*) the effect of compression rate on the π-A isotherm; (*b*) pressure relaxation following compression to preselected film pressures; and (*c*) surface hysteresis as affected by repeated cycling and minimum area of compression.