

September 28, 2018

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RE: PF 44(4) In-Process Revision: <659> PACKAGING AND STORAGE REQUIREMENTS
Correspondence Number—C199320

On behalf of the Consumer Healthcare Products Association (CHPA), a 137 year-old trade association representing the nation’s leading over-the-counter (OTC) medicine and nutritional supplement manufacturers, we would like to comment on the in-process revision of <659> including the references to USP chapters <661>, <661.1>, and <661.2>.

The proper application/usage, scope, and cause for revisions of the <661> suite of chapters is not clear nor intuitive which is a concern given the potential impact. There are unanswered questions concerning the relation to existing FDA/CDER and FDA/CFSAN guidance and regulation.

The industry requests another draft be published in PF after a Product Quality Research Institute workshop is held to consider broader input. The workshop will focus on a review of revised regulations including presentations from USP, industry and discussions concerning regulatory perspectives. Sessions are also planned to discuss preparing for drug product testing implementation and analytical strategies. The output from the workshop could include a white paper and/or a follow-up workshop.

As you know CHPA supports improving compendial methods and establishing product standards which can provide an additional measure of safety for OTC products. We look forward to developing a workshop to help the industry understand why the USP expectations have changed; help USP understand the substantial impact to the industry and hear from FDA about their experiences with addressing patient safety so that a process for implementation can be presented to the public as a recommended path forward.

Usage Concerns:

The USP documentary standards are continually in a state of revision with variance in impact across the industry. Some updates are relatively minor while others can be quite significant and still others might not represent a consensus. We understand that the <661> suite of chapters are not in a final state and since these will have major impact across the industry, USP should reconsider an implementation date. Without finalizing these standards, even minor changes to

the chapters could have major impacts on testing or retesting costs. In addition to the deficiencies we list in the notes below, how the chapters are applicable to the packaging of low risk dosage forms is unclear.

We understand that the USP Expert Committee on packaging is still discussing the requirements for extractable metals testing in required for materials in <661.1>. If the manufacturer tests the current materials per the current <661.1> (as early implementation is allowed) and these tests are removed, it would result in a considerable waste of resources. Alternatively, retesting would have to be performed if the manufacturer does not test for all extractable metals that are listed in a final version.

Presumably the extractable metals test requirement in <661.1> is in place to screen the metals in each plastic material that will go into final packaging system and this would allow the manufacturer to assess the elemental impurity (EI) contribution from the packaging system to the final product. However, we have seen no justification for the limits/thresholds listed in <661.1> and appears to be inconsistent with ICH Q3D.

We are aware that not all suppliers are committed to test/comply with the requirements in <661.1>. We strongly encourage USP to work with suppliers when creating revisions to this chapter. Not only does USP have no justification for the reporting limits for the metals, reporting limits for the same metal are not consistent for different plastic materials listed in the chapters.

Scope Concerns:

USP should clarify how the requirements are applicable to packaging of low risk dosage forms or explain how low risk dosage forms are to be held to the same standard as other dosage forms. Both CDER* and CFSAN** have guidance for container closure systems and indirect food additives*** and it seems that CFSAN's approach to establish the safety of food packaging has low risk pharmaceutical packaging covered. What additional patient safety is established by implementing USP <661>?

*FDA/CDER/CBER, Guidance for Industry Container Closure Systems for Packaging Human Drugs and Biologics May 1999.

**FDA/CFSAN, *Recommendations for Chemistry Data for Indirect Food Additive Petitions*, Version 1.2, Chemistry Review Branch, Office of Pre-Market Approval, June 1995.

*** Guidance for Industry: Preparation of Premarket Submissions for Food Contact Substances (Chemistry Recommendations), December 2007.

We support excluding low risk drug products since exposure to impurities migrating from the plastic while consuming/using these medicines is no different than consuming foods. For a given plastic resin, exposure to impurities from the packaging is likely orders of magnitude higher from consuming foods than medicines and therefore the standards for foods should be significantly greater than for medicines. Assume for every gram of medicine consumed, the average person is consuming at least 1,000+ grams of food. In FDA's 'Container Closure' guidance, the work that CFSAN does to support packaging for food is recognized by CDER multiple times. These excerpts from the guidance clearly show extractables and leachable (E&L) studies typically not being necessary (this concept is NOT clearly mirrored in the USP text regarding the Chemical Safety Assessment) and reliance on CFSAN's indirect food additive regulations.

"For solid oral dosage forms, a reference to the appropriate indirect food additive regulation for each material of construction is typically considered sufficient evidence of safety. However, for a powder for reconstitution dosage form, reference only to the indirect additive food regulations as evidence of safety for the material of construction is not recommended. Compatibility for solid oral dosage forms and for powders for reconstitution is typically addressed for plastics and glass by meeting the requirement so USP Containers test."

"To address safety and compatibility, the results of extraction/toxicological evaluation studies should be provided for drug products that are likely to interact with the packaging components and introduce extracted substances into the patient...For drug products less likely to interact, other tests (e.g. USP Biological Reactivity Test) or information (e.g. appropriate references to the indirect food additive regulations at 21 CFR 174-186) could be used to address the issue of safety and compatibility. For example, an appropriate reference to an indirect food additive regulation is generally sufficient for a solid oral dosage form product."

CFSAN clears materials and additives for use in food packaging by way of companies submitting filings for approval for clearance to use the materials for food packaging in a similar fashion that pharmaceutical companies file drug products to CDER for approval. Part of the required data package are migration studies, which is a surrogate for E&L studies. Even when E&L studies are not performed, the use of the material is supported by the migration studies that were performed to have the material cleared for use.

Food and oral medicines both are consumed orally and therefore what is safe for food should be considered safe for medicines:

- 1) Humans consume significantly more food than medicines
- 2) Relative to solid oral dosage forms (SOD's), CFSAN does not require migration studies for packaging that is used with foods with no oil on the surface, because the risk of migration is so low, it is considered negligible and a default level of migration is assumed. The FDA's approach above suggests that E&L is not required for SODs as SODs would be analogous to a dry food without oil on the surface in most cases.

- 3) CDER guidance indicates that even for liquids, E&L studies are not required as long as the dosing regimen is acute and not long term. Also note the parallel to food in this excerpt.

“A patient’s exposure to substances extracted from a plastic packaging component (e.g., HDPE, LDPE, PP, laminated components) into a liquid-based oral dosage form is expected to be comparable to the patient’s exposure to the same substances through the use of the same material when used to package food. Based on this assumption, an appropriate reference to the indirect food additive regulations (21 CFR 174-186) is typically considered sufficient to establish safety of the material of construction. This assumption is considered valid for liquid-based oral dosage forms which the patient will take for only a relatively short time (acute dosing regimen).

Other notes:

1. In the Packaging section of General Chapter <659>, we are concerned about the proposed addition of references to general chapters <661.1> and <661.2> and would recommend maintaining the reference to chapter <661> only. As per chapter <1661>, “...the proper use and application of the <661> suite of chapters may not be intuitive to some stakeholders...”. The proposed language in this general chapter that “Any plastic material...must meet the applicable requirements of *Plastics Materials of Construction* <661.1>”, may be interpreted by some stakeholders that testing per <661.1> is required where results from <661.2> might be more appropriate for a given situation. Keeping the reference to <661> only allows users to follow the entire suite of chapters to determine the most appropriate testing for their needs. We recommend clarification of <659> to clearly state that it is applicable to all USP, NF articles and that <661.1> and <661.2> are applicable to drug products. In addition, <661.1> and <661.2> must be updated to clearly indicate that the chapters are applicable to plastic materials and the packaging systems used for drug products.
2. In the General Definitions section of General Chapter <659>, it is recommended to correct the reference within Tamper-evident packaging from “21 CFR §221.132” to “21 CFR §211.132”. 21 CFR §221 does not exist.
3. In the General Definitions section of General Chapter <659>, it is recommended to correct the reference within associated components to EXCLUDE dietary supplements from the requirement of metric units only.
4. In the General Definitions section of General Chapter <659>, we are concerned about the proposed reference to <661.2> to “Light-resistant container”. While light transmission testing for plastics containers is proposed in <661.2>, it is currently included in <671> and there is a separate light transmission method included in <660> for glass containers. The acceptance criteria are almost half of what is listed in <671> and what was proposed in PF 42(4). No justification for reducing the acceptance criteria to half was provided and this change was not vetted through PF for public comments

5. In General Chapter <659>, there is a section dedicated to the Poison Prevention Packaging Act that is administered by the CPSC and can be found in 16 CFR § 1700. We recommend that the USP consider simplifying this section to a reference to the CFR only. The USP does not control revisions to this act and may not be able to align timing of <659> revisions should substantive changes be made within the CFR (e.g. introduction of the Consumer Product Safety Improvement Act of 2008).
6. General Chapter <659> declares relative to temperature storage that other parameters may be used if supported by data collected by an organization. This same concept of selection (in this situation among the defined options) based on data in addition to a default, should align regarding the packaging requirements. It should be included in the Packaging section which currently states: *Every monograph in USP–NF must have packaging and storage requirements. For the packaging portion of the statement, the choice of “containers” is provided in this chapter. For active pharmaceutical ingredients (APIs), the choice would be a tight, well-closed, or, where needed, light-resistant container. For excipients, given their typical presentation as large-volume commodity items (packaging systems ranging from drums to tank cars), a well-closed container is an appropriate default requirement. Articles must be protected from moisture, freezing, and excessive heat (see General Definitions) when no specific directions or limitations are provided.*
7. Within the controlled cold temperature definitions, the proposed wording states that controlled cold excursions may only occur one time during possession of the product within the supply chain unless directed otherwise by the manufacturer. This sentence should be removed. The value of once is arbitrary and the loose framework around the concept of “supply chain possession” relative to the complex industry transportation structure for global organizations does not allow for feasible implementation of this concept relative to perceived value.

Best Regards,



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