Commentary

USP–NF 2023 Issue 1

November 1, 2022

In accordance with USP's *Rules and Procedures of the Council of Experts ("Rules*"), and except as provided in Section 9.02 *Accelerated Revision Processes*, USP publishes proposed revisions to the *United States Pharmacopeia and the National Formulary* (*USP–NF*) for public review and comment in the *Pharmacopeial Forum (PF),* USP's free bimonthly journal for public notice and comment. After comments are considered and incorporated as the Expert Committee (EC) deems appropriate, the proposal may advance to official status or be re-published in *PF* for further notice and comment, in accordance with the Rules. In cases when proposals advance to official status*,* a summary of comments received and the appropriate Expert Committee's responses, as well as Expert Committee-initiated changes, are published in the Proposal Status/Commentary section of USPNF.com at the time the official revision is published.

The *Commentary* is not part of the official text and is not intended to be enforceable by regulatory authorities. Rather, it explains the basis of Expert Committees' responses to public comments on proposed revisions. If there is a difference or conflict between the contents of the *Commentary* and the official text, the official text prevails.

For further information, contact:
USP Executive Secretariat
United States Pharmacopeia
12601 Twinbrook Parkway
Rockville, MD 20852-1790 USA

Comments were received for the following when they were proposed in Pharmacopeial Forum:

General Chapters

<432> Determination of Zeta Potential by Electrophoretic Light Scattering
<1042> Cell Banking Practices for Recombinant Biologics

Monographs

Acetyltriethyl Citrate
Albuterol Tablets
Alginic Acid
Amphetamine Sulfate Tablets
Artemether
Atomoxetine Hydrochloride
Calcium Propionate
Carboplatin Injection
Carteolol Hydrochloride
Chlorthalidone
Chlorthalidone Tablets
Curcuminoids Capsules
Curcuminoids Tablets
Cyclophosphamide Capsules
Dextrates
Dextrose and Sodium Chloride Injection
Dutasteride and Tamsulosin Hydrochloride Capsules
Emtricitabine
Fosamprenair Calcium Tablets
Hydrogenated Polydextrose
Linezolid Tablets
Maltodextrin
Meclofenamate
Pamidronate Disodium for Injection
Polyvinyl Alcohol
Potassium Alginate
Quinapril and Hydrochlorothiazide Tablets
Risedronate Sodium Delayed-Release Tablets
Rivaroxaban Tablets
Sodium Alginate
Tinidazole Tablets
Trazodone Hydrochloride Tablets
Triethyl Citrate
Valacyclovir Hydrochloride
Valganciclovir Hydrochloride
Valsartan Tablets

No comments were received for the following proposals:

General Chapters

<126> Somatropin Bioidentity Test
<345> Assay for Citric Acid/Citrate and Phosphate

Monographs
Aloe
Bael Tree Fruit
Bael Tree Fruit Dry Extract
Bael Tree Fruit Powder
Bifidobacterium Animalis Subsp. Lactis
Cetyl Palmitate
Conjugated Linoleic Acids-Free Fatty Acids
Demeclocycline
Lindane Lotion
Manganese Sulfate Injection
Polypropylene Glycol 11 Stearyl Ether
Sugar Spheres

General Chapters

General Chapter:	<432> Determination of Zeta Potential By Electrophoretic Light Scattering
Expert Committee:	General Chapters—Physical Analysis
No. of Commenters:	1

Development of the Method

Comment Summary #1: The commenter, referring to the use of term “micelle” in the “Determination of the Concentration Range” and “Method Validation” sub-sections suggested replacing that term with the term “particles.”
Response: Comment partially incorporated. The expert committee decided to replace the term “micelles” with the term “colloidal particles,” stating that the term “colloidal particles” more closely represents the physical reality of the subject probed by the scattering of light in the zeta potential measurement test.

General Chapters:	<1042> Cell Banking Practices for Recombinant Biologics
Expert Committee:	Biologics Monographs 2-Proteins
No. of Commenters:	11

General Comments

Comment Summary #1: The commenter recommended to indicate whether any particular statements are based on the CFR, FDA, or other guidelines, or if they represent solely the USP vision. References and clarifications should be provided in the text.
Response: Comment incorporated. References have been added to the reference list.
Comment Summary #2: The commenter suggested that key terms and definitions should be based on 21 CFR 600.3, FDA, WHO, and ICH guidance documents, and definitions should be added to the Glossary with references.
Response: Comment partially incorporated. Wherever possible, key terms in the Glossary were defined and referenced in accordance with established standards. There were also other terms used in the chapter that required definition, and therefore the USP Cell Banking Expert Panel and the BIO2-Proteins Expert Committee has defined the terms.
Comment Summary #3: The commenter recommended organizing the chapter in a more concise format, eliminating unnecessary repetitions in the text and figures.
Response: Comment incorporated. Several edits have been made to the chapter and figures to reduce repetition and enhance flow.
Comment Summary #4: The commenter suggested to separate information on mammalian and bacterial cell lines.
Response: Comment partially incorporated. Information on bacterial and mammalian cell lines has been separated, except in areas where there are commonalities to avoid repetition.
Comment Summary #5: The commenter suggested to remove the phrase “common practice” or adequately justify the use of the phrase.
Response: Comment partially incorporated. Most uses of “common practice” have been removed from the chapter. The remaining uses of “commonly used or common practice” are justified in the associated text when used in the chapter.
Comment Summary #6: The commenter suggested postponing publishing of USP chapter <1042> because ICHQ5A is cited several times, and several of the requirements are based on ICHQ5A, which is undergoing revision.
Response: Comment not incorporated. The timeline for revision and adoption of new version of ICHQ5A is unknown, and <1042> can be revised if the chapter has different requirements than the revised ICHQ5A. A statement has been added to the chapter to indicate that the chapter is consistent with current, R1, ICH Q5A. The chapter can be revised if needed when the revised version of ICH Q5A becomes official.
Comment Summary #7: The commenter suggested to align the phrase “recombinant biologics” used in the title and the phrase “biological drug product/biological product” used in the chapter.
Response: Comment incorporated. The definition of recombinant biologic was added to the Glossary to clarify this term.
Comment Summary #8: The commenter suggested to insert bacterial seed in scope of chapter <1042> because USP chapter <1238> refers to <1042> for information on bacterial seeds.
Response: Comment partially incorporated. USP will remove reference to <1042> from <1238>.
Comment Summary #9: The commenter suggested to cite ICH Q5A in Tables 3 and 4 instead of repeating content that may change in the update of ICH Q5A.
Response: Comment partially incorporated. A footnote was added that states, “For more information see current version of ICHQ5A. ICHQ5A is under revision during development of this chapter. The table is aligned with the current R1 version of ICHQ5A.”
Comment Summary #10: The commenter suggested to add guidance where the repetition for LIVCA (limit of in vitro age) studies are considered necessary.
Response: Comment not incorporated as there is adequate information in the chapter about when the testing of LIVCA may be necessary.

Introduction

Comment Summary #11: The commenter requested that the risk factors for cell line banking be revised in accordance with 21 CFR 610.18 and FDA/ICH guidelines as the list of risk factors is too broad.
Response: Comment partially incorporated. The intent of the list of risk factors was to provide broad summary information, so the list of risk factors was not revised, but guidances have been referenced, so users of the chapter can find the specific information. The following statement was added after the bulleted list: “See ICH and appropriate FDA guidelines for more specific information.”
Comment Summary #12: The commenter proposed to omit “process validation” as a quality risk factor.
Response: Comment not incorporated. The intent of the list of risk factors was to provide broad summary information. It is beneficial to consider process validation as a risk factor as material or samples may need to be set aside.

Scope

Comment Summary #13: The commenter suggested changing the text, “manufacturing drug substances for clinical and commercial applications” to “drug substances for commercial applications” in the sentence: “Each GMP cell bank should be tested and characterized to satisfy quality standards for identity, purity, and genetic stability and ensured to be free from adventitious contaminants for use in manufacturing drug substances for clinical and commercial applications.”
Response: Comment incorporated. The text was changed to “drug substances for commercial applications” as the commenter suggested in the above sentence.
Comment Summary #14: The commenter suggested deleting “patient bank” from the following sentence: “During the development phases, the bank can be released before it is fully tested to start drug substance manufacturing; however, the bank has to be fully tested for safety (identity, purity, free from adventitious contaminants) prior to a drug substance's release for patient bank clinical applications.”
Response: Comment incorporated. The term “patient bank” was deleted.
Comment Summary #15: The commenter suggested requirements for genetic stability should be considered, as appropriate, prior to commercial application.
Response: Comment not incorporated. Describing when genetic characterization, including genetic stability should not be specifically outlined in the chapter, as this testing may need a flexible approach.
Comment Summary #16: For clarification, the commenter suggested to add the words “conditionally and at risk to the following sentence: “The bank can be **conditionally** released, **at risk**, before it is fully tested to start drug substance manufacturing.”
Response: Comment incorporated. The words “conditionally” and “at risk” were added to the sentence: “The bank can be **conditionally** released, **at risk**, before it is fully tested to start drug substance manufacturing.”
Comment Summary #17: The commenter suggested to add the term “patient bank” to the Glossary.
Response: Comment not incorporated. The term “patient bank” was removed from the sentence: “The bank can be released before it is fully tested to start drug substance manufacturing; however, the bank has to be fully tested, especially for safety prior to a drug substance's release for patient bank clinical applications.”

General Processes and Considerations of Cell Banking

Comment Summary #18: The commenter suggested to clarify in the text that replacement Working Cell Banks (WCBs) are produced to ensure continuity of drug substance supply and replenishment of WCB is based on use, not necessarily when the biologic is approved.
Response: Comment incorporated. The text will be changed to, “To ensure a consistent supply, it is generally recommended that additional replacement WCBs be produced, as needed, once a biologic is approved for marketing.” To clarify that the replacement of WCBs is when needed and not necessarily when the product is approved.
Comment Summary #19: The commenter recommends mentioning the stability in the list of criteria for replacement WCBs.
Response: Comment not incorporated. Storage stability is listed under Replacement Working Cell Bank in Figure 2, so additional text is not needed.
Comment Summary #20: The commenter requested to include where the source, origin, generation, propagation, and selection of the cell line should be documented.
Response: Comment not incorporated. The chapter’s objectives include best documentation practices, but specifying where to document the information is outside these objectives.
Comment Summary #21: The commenter recommended to clarify or refer to the purity testing for pmRCB to ensure completeness of guidance.
Response: Comment not incorporated. Purity testing of the pmRCB is discussed later in the chapter.
Comment Summary #22: Several commenters suggested to move the bar at the right side of Figure 1 that indicates the use of Good Manufacturing Process to start at “culture premaster research cell bank (pmRCB) into Master cell bank (MCB)”. One commenter also suggested to revise Figure 1 and 2 to ensure consistency between the text and the figures.
Response: Comment incorporated. In Figure 1, the bar that indicates the use of Good Manufacturing Processes was moved to start at the fifth box down from the top, "Culture premaster research bank (pmRCB) into Master cell bank (MCB), growth characteristics, media, raw material qualification, cell density, viability and process development.” This sentence was added, “Need to have documentation that allows RCB to be accepted and moved into GMP.”
Comment Summary #23: The commenter recommended in Figure 1 to remove the bar or split in GMP and non-GMP according to the text in the document and figure 2. The commenter indicated that Figure 1 is conflicting with Figure 2 and the text in the document, which (correctly) states that activities from MCB manufacture onwards should be performed in a GMP environment.
Response: Comment incorporated. In Figure 1, the bar that indicates the use of Good Manufacturing Processes has been moved to start at the fifth box down from the top, "Culture premaster research bank (pmRCB) into Master cell bank (MCB), growth characteristics, media, raw material qualification, cell density, viability, and process development.”
Comment Summary #24: The commenter suggested to combine Figures 1 and 3, and to correct that GMP conditions are required before the pre-MCB stage.
Response: Comment partially incorporated. Figure 1 is meant to be broad, and subsequent figures are meant to provide more specific detail, so Figures 1 and 3 will not be combined. Figure 1 has been corrected to indicate that the use of Good Manufacturing Processes is not required in the pre-MCB stage.
Comment Summary #25: The commenter recommended removing the following text,"… which need to go through purity testing prior to the production of MCBs and subsequent WCBs" because not all of the details of the testing are discussed.
Response: Comment not incorporated. The details are discussed later in the chapter and are not needed in this section.
Comment Summary #26: The commenter suggested adding the words, “as needed” to the following sentence: "To ensure a consistent supply, it is generally recommended that additional replacement WCBs be produced **as needed** once a biologic is approved for marketing."

Response: Comment incorporated. The words “as needed” were added to this sentence: “To ensure a consistent supply, it is generally recommended that additional replacement WCBs be produced **as needed** once a biologic is approved for marketing."
Comment Summary #27: The commenter recommends that Section 2 of the chapter be revised and expanded in accordance with ICH Q5D.
Response: Comment partially incorporated. A reference to ICH Q5D has been added instead of re-stating what is in the guidance.
Comment Summary #28: The commenter suggested defining the terms “production cell line” and “premaster research cell bank (pmRCB)”.
Response: Comment incorporated. The terms are defined in the Glossary for clarification.
Comment Summary #29: The commenter suggested to add “premaster research cell bank” to the Glossary.
Response: Comment incorporated. The term “premaster research cell bank” is defined in the Glossary.
Comment Summary #30: The commenter suggested changing the word “purity” to “clonality” in Figure 1.
Response: Comment not incorporated. “Purity” is specifically meant as the purity needs to be tested before moving into a GMP facility.
Comment Summary #31: The commenter recommended to remove the text, “evaluation of the integrity and stability of those genes for the intended purposes should be included as a part of the cell substrate characterization” because this characterization is not always done.
Response: Comment not incorporated. The term, “should” in the statement, “evaluation of integrity should be included in characterization” provides some flexibility; however it is strongly recommended to evaluate integrity.
Comment Summary #32: The commenter requested to remove the requirement to test the purity of the pmRCB before the production of MCBs and subsequent WCBs.
Response: Comment not incorporated. Although purity testing is not a requirement included in regulatory guidances, purity testing is usually required to take a product into a GMP setting. The purity testing is included in this above 1000 general chapter with the intent to provide information in addition to what can be found in regulatory guidance.
Comment Summary #33: The commenter requested to clarify how stability should be tested.
Response: Comment not incorporated. Stability testing can be product specific and appropriate testing may change throughout phases of development which is why it is not included in the chapter. ICH documents can be referenced for guidance on stability testing.
Comment Summary #34: The commenter suggested to change to the wording to indicate purity testing of the RCB or handling the RCB under quarantine followed by purity testing of the MCB.
Response: Comment partially incorporated. Sterility is a risk when moving into a GMP facility, so this text was added to the chapter: “Appropriate qualification testing of RCB is recommended to be performed prior to moving into GMP.”

PRODUCTION CELL LINE/STRAIN DEVELOPMENT AND RCB GENERATION

3.1 Common Cell Line Types and Associated Expression Constructs

Comment Summary #35: Commenter recommends adding references to original publications that cover the historical information and properties of common CHO cell lines and *E. coli* strains.
Response: Comment not incorporated. The current references provide information about the CHO cell lines and E. coli strains.
Comment Summary #36: The commenter recommended adding to the general information list that ease of engineering may be enabled by availability of a fully elucidated CHO genomic sequence.

Response: Comment not incorporated. It is not necessary to state that the CHO genomic sequence is fully elucidated because the availability of the CHO genomic sequence can be considered common knowledge.
Comment Summary #37: The commenter recommended to add the following reference: 'Frye et al; Biologicals Volume 44, Issue 2, March 2016, Pages 117-122'.
Response: Comment incorporated.
Comment Summary #38: The commenter suggested adding information about additional testing considerations that are needed when retroviruses (e.g., lentiviruses) are used to insert the gene of interest.
Response: Comment partially incorporated. A statement about the use of retroviruses was included, but the topic will not be added to the chapter, as the use of retroviruses would need additional conversation with the appropriate regulatory authority.
Comment Summary #39: The commenter suggested making changes to the text to indicate that changing cell lines during drug development is not common.
Response: Comment partially incorporated. Changes were made to reflect that it is not common practice to change cell lines during drug development. This sentence was added: "In addition, comparability and other product impacts should be evaluated."
Comment Summary #40: The commenter suggested that the statement, "CHO cells have the capacity for efficient, post-translational modifications, such as glycosylation, which enable the CHO-derived therapeutic proteins to be" needs to have more text added to the end of the sentence.
Response: Comment not incorporated. The full sentence in the document is a complete statement, "CHO cells have the capacity for efficient, post-translational modifications, such as glycosylation, which enable the CHO-derived therapeutic proteins to be both compatible with and bioactive in humans."
Comment Summary #41: The commenter suggested changing "non-secreting (NS0) mouse myeloma cells" to "non-IgG secreting (NS0) mouse myeloma cells".
Response: Comment not incorporated. The change was not made because the NS0 cells can secrete things other than IgG.
Comment Summary #42: The commenter suggested to remove the detailed annotation of the GOI and the description of cloning.
Response: Comment not incorporated. The annotation of the GOI and the description of cloning aligns with what is in ICH Q5B.
Comment Summary #43: The commenter requested clarification of the benefit of CHO cell use and the ability to integrate DNA to generate stable recombinant protein expressing cell lines.
Response: Comment not incorporated. The text clearly explains the benefit of using CHO cells. CHO cells have the capacity for efficient, post-translational modifications, such as glycosylation, they are able to adapt and grow suspension culture and have a lower adventitious virus safety risk.
Comment Summary #44: The commenter suggested to add the word "commercial" to the sentence "All CHO cell substrates used for commercial recombinant protein production are expected to be single-cell derived." as there may be cases where cells are pooled.
Response: Comment partially incorporated. The word "commercial" was added to the sentence. Discussion of pooling cells is a business and scientific risk consideration, and it is out of scope of the chapter to provide such guidance.
Comment Summary #45: The commenter suggested the following edits to the sentence: "Selection of recombinant cell lines ~~is~~ **can be** performed using stepwise increases in the media concentration of MTX, which results in amplification of the transfected DHFR gene together with the GOI, ~~consequentially~~ **possibly** increasing the productivity of the GOI." because many companies have worked on strategies that omit the MTX.
Response: Comment incorporated. The suggested edits to the sentence were incorporated.

Comment Summary #46: The commenter suggested the following edits to the sentence: "Expression plasmids are **often** linearized prior to transfection and are **generally** integrated into the CHO host cell genome by random integration." because linearization is not a prerequisite for random integration.
Response: Comment incorporated. The sentence was edited by adding the words "often" and "generally" to the sentence.
Comment Summary #47: The commenter suggested the following edits to the sentence "Therefore, evaluation of the integrity and stability **of the overexpressed genes** for the intended purposes should be included as a part of the cell substrate **genetic stability** characterization. **In addition, knocked out genes should be characterized**." The commenter also suggested including a statement about genes that have been knocked out.
Response: Comment incorporated. The sentence was edited as the commenter suggested. A statement that indicated that knocked out genes should be characterized was also included.
Comment Summary #48: The commenter suggested to make Table 1 more Cell Banking focused as the table is focused on choosing an expression system.
Response: Comment partially incorporated. Table 1 is intended to be an example of original choice of cell line. The title of Table 1 was changed to "Comparison of two Common Cell Substrates for Recombinant Therapeutic Products" to clarify the purpose of the table.
Comment Summary #49: The commenter suggested changing "**primary, secondary and tertiary**" to "higher order structure". The sentence will now read, "Secreted recombinant proteins are properly folded and are identical in higher order structure to the natural human protein".
Response: Comment incorporated. The suggested edit of using "higher order structure" was incorporated.
Comment Summary #50: The commenter recommended adding the word chromosomes to the sentence: "New chromosomal structures, known as homogeneously staining regions (HSRs), can be found in the metaphase **chromosomes** of MTX-selected CHO cells".
Response: Comment incorporated. The word "chromosomes" was added to the sentence.
Comment Summary #51: The commenter suggested to add "antibiotic resistance genes that are sometimes used for CHO cells, (e.g., neomycin, bleomycin)" to the sentence: "Selection markers such as DHFR or GS for recombinant cell line selection."
Response: Comment partially incorporated. The phrase, "the commonly used" was added to the sentence: "Selection markers such as **the commonly used** DHFR or GS for recombinant cell line selection" because the list of selection markers is not meant to be an exhaustive list.
Comment Summary #52: The commenter requested that text be added to clarify the characterization process as to whether the knock-in or knock-out has to be characterized in every cell line made using that host or just once for the host cell line.
Response: Comment not incorporated. Text is clear as written. Cell substrate characterization only refers to new genes knocked out or over expressed. The location in the text indicates this.
Comment Summary #53: The commenter requested to clarify copy number considerations regarding stability.
Response: Comment not incorporated. Copy number alone is not stability indicating.
Comment Summary #54: The commenter requested to clarify antibiotic use.
Response: Comment not incorporated. The text is clear about the use of antibiotics because the use of antibiotics in production systems are not recommended.

3.2 PRODUCTION CELL LINES/STRAINS AND RECOMMENDED DOCUMENTATION

Comment Summary #55: The commenter suggested to replace the word "purity" with "strain ID" in the sentence: "Cell line purity can be assessed with PCR or using short tandem repeat (STR) profiling or DNA fingerprinting or another appropriate technology to verify the identity of the host cells."

Response: Comment incorporated. The word “purity” was replaced with “strain ID”.
Comment Summary #56: The commenter requested clarification because the phrase “RCBs are thawed and expanded to generate the pm RCB” implies that it is a prerequisite to generate a pmRCB, but it is not a perquisite.
Response: Comment incorporated. The phrase “or MCB as appropriate” will be added to the end of the sentence: “Once the final production strains/cell lines are identified, the corresponding RCBs are thawed and expanded to generate the pmRCB.”
Comment Summary #57: The commenter suggested edits to the following sentence: “Because the **RCB**/pmRCB is usually generated in a non-GMP facility, **it is recommended that RCB/**pmRCBs from mammalian cell lines should be tested and found sterile for contaminants and negative for mycoplasma before transfer to a GMP facility for the generation of the MCB”
Response: Comment incorporated. The suggested edits were made to the sentence.
Comment Summary #58: The commenter suggested removing the testing of purity on MCB and WCB as purity testing may be a recommendation for business-critical reasons, but not a quality requirement.
Response: Comment not incorporated. The chapter provides recommendations and describes best practices which includes testing the purity of the MCB and WCB.
Comment Summary #59: The commenter suggested the following edits to the sentence: “For an *E. coli* derived **RCB/**pmRCB, testing for purity, identity, and bacteriophages **is recommended** before entry to a GMP facility.”
Response: Comment incorporated. The suggested edits of adding “RCB” and the phrase “is recommended” have been added to the sentence.
Comment Summary #60: The commenter suggested adding language to indicate that the post-banking evaluation of the RCB/pmRCB for growth, viability, and viable cell density to aid MCB production and characterization is recommended but not a requirement.
Response: Comment not incorporated. Post-banking evaluation of the RCB/pmRCB for growth, viability, and viable cell density is a requirement. RCB will be added before the pmRCB.
Comment Summary #61: The commenter requested to clarify components referenced.
Response: Comment not incorporated. The Expert Panel and Expert Committee decided it was not necessary to show how to describe components.
Comment Summary #62: The commenter requested to clarify when and how pmRCB testing can be accomplished.
Response: Comment not incorporated. Timing is specified as before entering GMP. The chapter does not need to be more specific about timing.
Comment Summary #63: The commenter requested to clarify DMSO use and hold time determination.
Response: Comment not incorporated. The DMSO hold time is specific for each cell line.
Comment Summary #64: The commenter requested to clarify "appropriate storage conditions".
Response: Comment partially incorporated. A reference to USP chapter <1044> *Cryopreservation of Cells* was added.
Comment Summary #65: The commenter suggested the following edit to the statement, “Figure 4 shows an example of a cell **banking** process for a mammalian (CHO) cell bank”.
Response: Comment incorporated. The word “banking” was added to the sentence.
Comment Summary #66: The commenter suggested to add text to indicate that mammalian cell banks are typically kept in at least two different geographical locations.
Response: Comment incorporated. This text was added to the chapter: “To avoid any unexpected loss of the cell bank, the containers are typically kept in at least two different geographical locations.”

Comment Summary #67: The commenter requested clarification of EOP cells and at the limit of in vitro cell age production and testing for Figure 3 since EOP and LIVCA cells may not be the same (different timelines may be present).
Response: Comment incorporated. End of Process (EOP) was spelled out in the last box of Figure 3 to specify production and testing of End of Process cells at the limit of in vitro cell age (LIVCA).
Comment Summary #68: The commenter requested clarification about what should be added to the label. The following edits are suggested: "Label the vials in advance with **the appropriate information** (e.g., cell bank lot number, tube number, and production date)."
Response: Comment incorporated. The phrase “the appropriate information” was added to the sentence.
Comment Summary #69: The commenter suggested changing the word “usually” to “may” in the following sentence: “During development, the production strains/cell lines used for manufacturing clinical materials **may** continue to evolve to meet the commercial manufacturing needs.”
Response: Comment incorporated. The word “usually” was changed to “may” in the sentence.
Comment Summary #70: The commenter suggested to remove cDNA copy number from the section on *Specification Analysis* in Figure 4.
Response: Comment partially incorporated. The title of the section was changed, so it does not read *Specification Analysis* as *Plasmid copy number* is incorporated in Figure 4 as an additional test, not for specification.
Comment Summary #71: The commenter requested clarification of the appropriate cleanroom quality control procedures.
Response: Comment not incorporated. It is the responsibility of each company to determine cleanroom procedures with their quality assurance.
Comment Summary #72: The commenter suggested to add “and cell density” to the end of the sentence: “Fill freezing containers to appropriate volume” in Figure 4.
Response: Comment incorporated. The phrase “and cell density” was added to the sentence.
Comment Summary #73: The commenter requested clarification of the distinction between cell bank characterization tests and tests required for release based on a specification in Figure 4.
Response: Comment incorporated. The title, *Specification Analyses* was removed from Figure 4, and the text in the box in Figure 4 was replaced with "Refer to Table 3 for release testing and additional testing for characterization”.
Comment Summary #74: The commenter requested to delete the mention of cleanroom procedures.
Response: Comment not incorporated. It is the responsibility of each company to determine cleanroom procedures with their quality assurance.
Comment Summary #75: The commenter recommended to align the glycerol concentrations, ”Mix with “87%” glycerol” in the process flow text that mentions 20-30% glycerol. The commenter also suggested to provide example of in-process control.
Response: Comment incorporated. Remove “87%” from Figure 5. The “87%” is the stock used and the final concentration should be 20-30%. Text has been added to the Figure to provide example of in-process control.
Comment Summary #76: The commenter recommended removing the “87%” concentration from Figure 5.
Response: Comment incorporated. The “87%” concentration was removed.
Comment Summary #77: The commenter recommended removing the “87%” concentration from the Figure 5.
Response: Comment incorporated. “87%” was removed from Figure 5.
Comment Summary #78: The commenter recommends that the following two sentences be moved to the sub-section *Additional Considerations*: "To avoid any unexpected loss of the cell

bank, the containers are typically kept in at least two different geographical locations. During transportation, the containers are shipped and are continuously monitored for temperature to confirm that they remain acceptably frozen."
Response: Comment incorporated. The two sentences were moved to the section *Additional Considerations*.

ADDITIONAL CONSIDERATIONS

Comment Summary #79: The commenter suggested to change “new pre-and post-launch cell lines” to “clinical” and “commercial” cell lines, respectively.
Response: Comment partially incorporated. The phase “pre- and post-launch” will be removed, so it will read: “The new cell lines may be from a new species (e.g., a change from NS0 to CHO) or from the same species with additional genetic modifications to improve the cell culture performance and/or the quality/productivity of the therapeutic proteins.”

4. CLONALITY

Comment Summary #80: The commenter recommended changing the title of the section to "Mammalian Cell Line Clonality”. And to add the following statement: "This section discusses clonality of production cell lines-derived from mammalian cells."
Response: Comment incorporated. The section title was changed, and the statement was added.

4.1 OVERVIEW

Comment Summary #81: The commenter suggested changing “limited dilution” to “limiting dilution” in the sentence: “These practices include limiting dilution, fluorescence-activated cell sorting”.
Response: Comment incorporated. “Limited dilution” was changed to “limiting dilution.”
Comment Summary #82: The commenter suggested adding the following phrase, “acquiring images of the single cell at Day 0 and on subsequent days to follow the outgrowth of the clones” to the sentence: “The supplemental evidence for the single-cell derivation of the cell line can be based on the use of a qualified imaging system, acquiring images of the single cell at Day 0 and on subsequent days to follow the outgrowth of the clones”.
Response: Comment incorporated. The phrase that the commenter suggested was added to the sentence.
Comment Summary #83: The commenter indicated that it is general when images are used as supportive information in the following statement from the General Chapter, “Images are evaluated for quality—based on criteria including image focus and clarity, cell shape, lack of debris or artifacts in the well—as well as for conformation that the entire well was captured in the image”
Response: Comment not incorporated. The commenter’s position was considered; no requested change was specifically identified.
Comment Summary #84: The commenter requested to omit the section “Other Automated Clone Selection Technology” because the section is very focused on high-speed laser manipulation methods.
Response: Comment partially incorporated. A sentence has been added to clarify the text contains one example, other methods can be used.

4.2 METHODOLOGY

LIMITING DILUTION CLONING

Comment Summary #85: The commenter suggested to include seeding density considerations.
Response: Comment partially incorporated. This sentence “The appropriate number of rounds (e.g., 2 rounds) at an appropriate seeding density” was added for clarity.
Comment Summary #86: The commenter suggested to delete 96 well plates, or modify language to allow flexibility for 384 well plates.
Response: Comment incorporated. 96-well plates were deleted.
Comment Summary #87: The commenter requested to add clarifying language on the use of fluorescence imaging the process as many production cells do not express fluorescent markers**.**
Response: Comment partially incorporated. The phrase “as applicable” was added to the fluorescence imaging.
Comment Summary #88: The commenter suggested to add the text, “Any reagent” used in the selection process should be tested for adventitious agents.
Response: Comment partially incorporated. The phrase “any reagent” was not added. The following text was added to the chapter, “Any biologically derived agent should be tested for adventitious agents. For example, if antibodies used…. “
Comment Summary #89: The commenter recommended deletion of this statement, “The process can be completed in as little as 7 days, with the identification of stable clones by 4 weeks.” because the timelines are subjective.
Response: Comment partially incorporated. The sentence was not deleted, but clarifying language was added. The process **in some cases** can be completed in as little as 7 days, with the identification of stable clones by 4 weeks.
Comment Summary #90: The commenter suggested a revision to exclude single cell printing.
Response: Comment partially incorporated. The phrase “commonly used” was removed to indicate that single cell printing is not commonly used.

4.3 ASSURANCE OF CLONALITY

Comment Summary #91: The commenter suggested to remove the text, “When probability calculations are included, they should be done so prospectively.” as this is not the practice used by the commenter.
Response: Comment not incorporated. The commenter’s position was considered, and the existing language reflects only that these are commonly used practices when probability calculations are included.
Comment Summary #92: The commenter suggested to remove "consistent process and PQ" as it does not seem to fit in this section.
Response: Comment not incorporated. The commenter’s position was considered, and the existing language reflects that these are common practices for assurance of clonality.
Comment Summary #93: The commenter suggested to remove reference to Southern blotting as the Southern blot does not provide much information on clonality.
Response: Comment incorporated. The reference to Southern blotting was removed.

5. CELL BANK CHARACTERIZATION

Comment Summary #94: The commenter suggested to revise the introductory paragraph of this section to remove statements such as “inherently variable”.
Response: Comment incorporated. The text was edited to remove “inherently variable”.

Comment Summary #95: The commenter suggested that genetic stability and characterization should be done beyond end of production.
Response: Comment not incorporated. The language in the chapter is appropriate to allow flexibility for testing beyond a typical manufacturing process.

5.1 CELL BANK QUALIFICATION AND CHARACTERIZATION

Comment Summary #96: The commenter suggested switching Section 5.1 and section 5.3 in the chapter to improve the flow of the chapter.
Response: Comment incorporated. Sections 5.1 and 5.3 were switched to improve the flow of the chapter.
Comment Summary #97: The commenter suggested combining sections 5.2 and 5.3 or better define the purpose of each section.
Response: Comment not incorporated. Sections 5.1 and 5.3 will be switched which will improve the flow of the chapter and redundancies will not be an issue.
Comment Summary #98: The commenter requested to delete restriction analysis map and plasmid stability are not listed as specification analyses in Table 3.
Response: Comment incorporated. Text from the box has been deleted.
Comment Summary #99: Commenter suggested adding information about monitoring genetic stability of cell banks under long term storage to sub-section 5.1.
Response: Comment not incorporated. The testing of LIVCA genetic stability is sufficient to cover stability of banks under long term storage.
Comment Summary #100: The commenter suggested to exclude NGS from section 5.1 or if NGS is kept, to provide guidance on the NGS data that is submitted or what comparisons are made.
Response: Comment partially incorporated. The statement has been revised to clarify that NGS is not one of the most common methodologies. The following edits has been made: “The most common methodologies for the assessment of gross structure of the expression construct are restriction endonuclease (RE) mapping analysis. DNA sequencing (NGS) is beginning to be used for genetic characterization.”
Comment Summary #101: The commenter suggested including a reference to PDA Technical Report 71 Emerging Methods for Virus Detection.
Response: Comment not incorporated. The expert committee did not agree with the commenter that the PDA reference was appropriate for discussion of genetic characterization.
Comment Summary #102: Commenter suggested to include that NGS should occur on cells at a representative cell age from a representative commercial process.
Response: Comment not incorporated. NGS is not being used for this purpose.
Comment Summary #103: Commenter recommended to reference to PDA Technical Report 71 Emerging Methods for Virus Detection.
Response: Comment not incorporated. The expert committee did not agree with the commenter that the PDA report was appropriate for genetic characterization.
Comment Summary #104: Commenter suggested to clarify what qualifies End of Production (EOP) cells to be analyzed and provide a worse-case scenario.
Response: Comment not incorporated. EOP can be cultured as long it needs to be for each user of the general chapter’s process.
Comment Summary #105: The commenter suggested to correct the improper use of an acronym: Next generation sequencing (NGS) of DNA.
Response: Comment incorporated. The improper use of the acronym was corrected to Next Generation Sequencing (NGS).

Comment Summary #106: The commenter suggested referencing PDA Technical Report 71 Emerging Methods for Virus Detection.
Response: Comment not incorporated. The PDA technical report is not an appropriate reference for this section as the scope of the document is safety and adventitious agents.
Comment Summary #107: The commenter suggested revising section 5.1 for clarity.
Response: Comment not incorporated. The commenter's position was considered, and the expert committee identified that no additional information was needed for clarity.
Comment Summary #108: The commenter recommended to clarify that lytic phage contamination is different from lysogenic phage contamination. Alternatively, reference a suitable paper or guidance to delineate the differences.
Response: Comment not incorporated. The type of phage contamination referenced by the commenter is too specific for inclusion in this chapter.
Comment Summary #109: The commenter recommended to include a discussion of risk-based approach in the Cell Bank Characterization section.
Response: Comment not incorporated. Risk based approach is not needed at the characterization stage. Characterization should be exhaustive as possible and not risk based. Risk based information is already included in chapter.
Comment Summary #110: The commenter requested to clarify that genetic characterization should be on the Master cell bank or the Working Cell Bank, but both are not necessary.
Response: Comment partially incorporated. Genetic characterization of the Master cell bank is always needed, and a comparison of the Working Cell Bank is optional and only done if necessary. The following edits have been made, "Genetic characterization is performed on samples taken at EOP and compared to the MCB. **If necessary, WCB could be tested with bridging to the MCB**."
Comment Summary #111: The commenter requested clarification as to if the chapter is specifying different sequencing than what is described in ICH Q5B.
Response: Comment not incorporated. The chapter cites ICH Q5B, and the user should follow ICH Q5B.
Comment Summary #112: The commenter suggested to add the word "identical" to the following sentence: "DNA sequence and RE pattern of the EOP cells at LIVCA should be **identical** to those of the MCB and/or the WCB."
Response: Comment not incorporated. The commenter's position was considered, and the expert committee identified that no additional information was needed for clarity.
Comment Summary #113: The commenter requested clarification on if NGS is a common DNA sequencing approach.
Response: Comment incorporated. NGS is not a common approach. Edits have been made to the chapter so that sequencing can be done with any platform.

5.2 MAMMALIAN CELL BANK TESTING

Comment Summary #114: The commenter suggested to remove "the same copy number" from the following sentence: "For an engineered cell line, the inserted GOI should remain intact and at the same copy number". The commenter suggested replacing "same" with "at a like".
Response: Comment partially incorporated. The following edits are made, "For an engineered cell line, the inserted GOI should remain intact and ~~at a consistent~~ copy number **should be determined to support consistent production**.
Comment Summary #115: The commenter requested clarification on whether or not the Master cell bank should comply with the test for hemadsorbing extraneous agents. The commenter also suggested including references for this test.

Response: Comment partially incorporated. The following sentence has been revised for clarification, “The MCB should also be assessed by the in vitro virus assay with the two endpoints of cytopathic effect and hemadsorption.”

Comment Summary #116: The commenter recommended that the chapter provide guidance that is clear and consistent on the situations where LIVCA studies are considered necessary and should be repeated. The commenter suggested the following edits, "The testing on LIVCA cells should be conducted for the initial MCB or WCB. When new WCB are expanded to or beyond the LIVCA, conduct testing to assess against the existing LIVCA."

Response: Comment partially incorporated. Two sentences with LIVCA were edited. "The testing on LIVCA cells should be conducted for the initial MCB or WCB. When new WCB are expanded to or beyond the LIVCA, testing should be conducted to assess against the ~~existing LIVCA~~ original MCB."

Comment Summary #117: The commenter suggested to clarify requirements for initial and future WCB. EOP testing is required for initial WCB but not for further/future WCBs.

Response: Comment not incorporated. Current text is consistent with ICH Q5A and ICH Q5A Table 1, Footnote F.

Comment Summary #118: The commenter suggested to delete the phrase, “using human cells with PERT as end point”, and to list only “Infectivity assay”

Response: Comment incorporated. ICH Q5A does not specify PERT as an endpoint.

Comment Summary #119: The commenter suggested to provide language that product-enhanced reverse transcriptase (PERT) assay (may not be needed if the cell line is known to express retroviruses [e.g., CHO/NS0 cell lines] and may be co-cultured with a relevant cell line depending on the test article.)

Response: Comment partially incorporated. The following text was deleted in the general chapter: “Product-enhanced reverse transcriptase (PERT) assay (may not be needed if the cell line is known to express retroviruses [e.g., CHO/NS0 cell lines] and may be co-cultured with human cell lines.)” The text was replaced with the following text: "If infectivity is not detected and no retrovirus or retrovirus-like particles have been observed by EM, reverse transcriptase (RT) or other appropriate assays should be performed to detect retroviruses that may be noninfectious."

Comment Summary #120: The commenter suggested to delete the phrase, “using human cells with PERT as end point”, list only “Infectivity assay”

Response: Comment incorporated. The phrase, “using human cells with PERT as end point” was deleted.

Comment Summary #121: The commenter indicated that “nucleic acid amplification test” may be used for specific contaminants using degenerate or specific primers.

Response: Comment not incorporated. New technology of nucleic acid amplification tests would need to be validated for use.

Comment Summary #122: The commenter indicated that comparability should be undertaken with ethical use of animals. It is not ethical to infect animals with viruses just for the sake of comparability.

Response: Comment not incorporated. The current version of ICH Q5A, cited in the general chapter, includes information on animal testing.

Comment Summary #123: The commenter requested further clarification on when the genetic characterization is performed.

Response: Comment partially incorporated. Text has been changed to clarify when genetic testing is performed. “Genetic characterization is performed on samples taken at EOP and compared to the MCB. **If necessary, WCB could be tested with bridging to the MCB**.”

Comment Summary #124: The commenter requested to change the text as to not specify the exact same copy number be achieved.

Response: Comment incorporated. The text was changed to, “For an engineered cell line, the inserted GOI should remain intact and ~~at a consistent~~ copy number should be determined to support consistent production.”

5.3 CELL BANK QUALIFICATION AND CHARACTERIZATION

Comment Summary #125: Commenter suggested specifying that purity testing be required for MCB and WCB in Table 3. The commenter also requested to clarify the difference between Specification Analysis and Additional Tests in Table 3.
Response: Comment partially incorporated. A footnote will be added to *Microbial Purity* under “Additional Tests” to specify that the purity test needs to be performed on EOP if not done in MCB and WCB. Specification tests are release tests; additional tests are characterization tests. A change was made to change “Additional Tests” to “Characterization Tests” for clarity.
Comment Summary #126: The commenter recommended that the following text be added to the last sentence of the first paragraph: “Use of each test should be agreed upon with the applicable health authority **and aligned with the latest version of the ICH Q5A guidance.**”
Response: Comment not incorporated. ICH Q5A is referenced several other places in the chapter. The use of each test needs agreement from applicable regulatory authority.
Comment Summary #127: The commenter suggested not to mention specific methods in Table 3 and that specific methods should not be specified as there are multiple appropriate methods. The commenter also requested clarification of the use of strain ID and nucleic acid profiling.
Response: Comment not incorporated. Table 3 is aligned with the current R1 version of ICHQ5. Strain ID is sequencing. Nucleic acid profiling is phenotype.
Comment Summary #128: The commenter suggested to remove DNA sequence or DNA sequencing from either list of specification tests or additional tests**.**
Response: Comment not incorporated. There is a difference between early (MCB and WCB) and late (EOP) stage and the testing performed. Characterization is more extensive in earlier stages. EOP is end of process and DNA sequencing can only be an additional test due to the stage of the cells.
Comment Summary #129: The commenter suggested to omit strain ID for the “Working Cell Bank” from Table 3.
Response: Comment incorporated. Strain ID for the “Working Cell Bank” was removed from Table 3.
Comment Summary #130: The commenter suggested to delete Table 3 and Table 4 and refer to guidance per current ICH Q5A.
Response: Comment not incorporated. Table 3 and Table 4 will be retained as these tables add value to the general chapter.
Comment Summary #131: The commenter suggested to edit Table 4 because it specifies the repetition of antibody production tests at EOP, which would exceed the existing guidance in ICHQ5A.
Response: Comment incorporated. The antibody tests in Table 4 have been updated to align with ICH Q5A. The Master cell bank (MCB) is only bank tested with the antibody production test.
Comment Summary #132: The commenter recommended to define similar terms in the Glossary at the end of the chapter.
Response: Comment not incorporated. The commenter’s position was considered and based on the scope and anticipated user of the general chapter, it was identified that additional definition was not necessary.
Comment Summary #133: The commenter suggested to remove the footnote a of Table 3 that specifies “only for bacterial cell banks” since the title of the table specifies bacterial cell banks.

Response: Comment incorporated. The footnote was removed from Table 3.
Comment Summary #134: The commenter suggested to update “antibody production tests” to align with ICH Q5A. The commenter also suggested to add “bar code assay” as a contemporary ID test to Table 4.
Response: Comment partially incorporated. Antibody tests at End of production (EOP) will be updated to align with ICH Q5A. The “bar code assay” comment was not incorporated. The bar code assay is captured within sequencing, so it will not be added to the table.
Comment Summary #135: The commenter suggested to update antibody production tests to align with ICH Q5A in Table 4.
Response: Comment incorporated. Antibody tests at EOP were updated to align with ICH Q5A.
Comment Summary #136: The commenter suggested to include assays for characterization of stability in Table 4.
Response: Comment not incorporated. Table 4 does not apply to genetic stability characterization. Genetic and cell line stability are normally separated**.**
Comment Summary #137: The commenter suggested to update Table 4 to align with ICH and FDA requirements or to rename Table 4 to be more specific about the types of characterization presented in the table.
Response: Comment partially incorporated. The title of the table has been updated to be more specific about the types of characterization presented in the table. Table 4 is aligned with the current R1 version of ICHQ5.
Comment Summary #138: The commenter requested that antibody production tests be recommended for MCB in Table 4 to align with current FDA and ICH guidance.
Response: Comment incorporated. The antibody production test has been updated to only be recommended for the Master cell bank in Table 4.
Comment Summary #139: The commenter suggested to add a footnote or asterisk to indicate that the requirement for testing of WCB and EOP for porcine or bovine contaminants is only required when bovine and porcine materials are being used to generate the banks.
Response: Comment incorporated. A footnote was added to indicate the contaminant testing is only necessary if bovine or porcine product used in development. The plus signed was changed to “if applicable” for the columns to indicate the testing is only performed in necessary.
Comment Summary #140: The commenter recommended to change the” –“to a “+” for Identity test for the MCB in Table 4 because ICH guidance requires identity tests for MCB.
Response: Comment incorporated. The minus sign was changed to a plus sign.
Comment Summary #141: The commenter suggested to fill in the blank spaces with a + or – where appropriate in Table 4.
Response: Comment incorporated. The negative sign was added to “Infectivity and Reverse transcriptase” assay.
Comment Summary #142: The commenter suggested to use category of tests (purity, identity etc.) in Table 4. Also, the commenter suggested to change additional tests to characterization tests.
Response: Comment not incorporated. There are multiple categories included in Table 4 that are accurate for the function of the tests.
Comment Summary #143: The commenter suggested that “Bovine and porcine virus in vitro assay” should be tested on the MCB only. The commenter also suggested that the test for virus should be related to what was used in the process**.**
Response: Comment incorporated. “Bovine and porcine virus in vitro assay” has been changed to “MCB +, WCB -, EOP” - A footnote has been added to specify that testing for viruses should be related to what was used in the process.
Comment Summary #144: The commenter suggested that the “Nucleic acid fingerprinting” should be required for MCB in Table 4.

Response: Comment incorporated. “Nucleic acid fingerprinting” was changed to indicate it was required.
Comment Summary #145: The commenter suggested to add a “-“ sign to WCB for Infectivity and Reverse transcriptase assay in Table 4.
Response: Comment incorporated. A minus sign was added to WCB for “Infectivity and the Reverse” transcriptase assay in Table 4.
Comment Summary #146: The commenter suggested to clarify requirements for initial and future WCB in Table 4. EOP testing is required for initial WCB but not for further/future WCBs.
Response: Comment not incorporated. Current text is consistent with ICH Q5A. User should review Q5A Table 1, Footnote F.
Comment Summary #147: The commenter suggested to add a “+” for Identity testing for MCB, and add a footnote to explain when identity testing may not be applicable in Table 4.
Response: Comment partially incorporated. In Figure 4, Identity for MCB has been changed to +; however, the footnote was not changed as the text in footnote c is consistent with ICH Q5A.
Comment Summary #148: The commenter suggested to add a footnote: “Bovine and porcine virus in vitro assay can be omitted for MCB, WCB and EOP if parental cell line used to generate MCB had been tested negative for Bovine and porcine viruses and no animal-derived raw material were used in transfection and subsequent steps leading to the generation of MCB and WCB as well as in the production of EOP”. If bovine and porcine raw materials were used but they have been sterilized by heat treatment or other means, there is no need to perform Bovine and porcine virus assay as well.
Response: Comment partially incorporated. MCB, WCB, and EOP were marked with a ‘-‘ for the Bovine and porcine virus in vitro assay. A footnote was added “When bovine and porcine raw materials are used these tests should be performed. Bovine and porcine virus in vitro Assay can be omitted for MCB, WCB and EOP if parental cell line used to generate MCB had been tested negative for Bovine and porcine viruses and no animal-derived raw material were used in transfection and subsequent steps leading to the generation of MCB and WCB as well as in the production of EOP.”
Comment Summary #149: The commenter suggested to specify the type of identity test described in Table 4 by indicating if the test is a cell line identity test or a species identity test. The commenter also recommended that the MCB should also be tested, so the commenter suggested changing the minus to a plus for MCB under the Identity test.
Response: Comment incorporated. The type of identity test was specified in Table 4, and the minus was changed to a plus for the MCB under the identity test.
Comment Summary #150: The commenter suggested to replace the plus with a minus for EOP for antibody production tests in Table 4.
Response: Comment incorporated. The plus sign was replaced by a minus sign for EOP in Table 4.
Comment Summary #151: The commenter suggested to omit the requirement to test for “Bovine and porcine virus” in vitro assay from the MCB, WCB and EOP in Table 4, as this test should not be made a requirement if the test article does not have a history with such materials.
Response: Comment incorporated. The requirement to test for Bovine and porcine virus in vitro assay from the MCB, WCB and EOP in Table 4 was removed.
Comment Summary #152: The commenter suggested to replace the minus with plus for the MCB in the Reverse transcriptase assay as the test is necessary for the MCB.
Response: Comment incorporated. The minus sign was changed to a plus sign for the MCB reverse transcriptase assay.
Comment Summary #153: The commenter suggested to move footnote “b” to Adventitious Virus Detection.

Response: Comment incorporated. Footnote 'b' was moved to Adventitious Virus Detection header.
Comment Summary #154: The commenter suggested adding NAT based testing as alternative to antibody production testing.
Response: Comment incorporated. A footnote was added, "alternative validated method (e.g., NAT) agreed upon with the regulatory authority may be used."
Comment Summary #155: The commenter suggested to mark a plus sign for Identity Tests for the MCB, and make WCB and EOP a minus sign.
Response: Comment partially incorporated. MCB has been changed to a plus sign. The commenter's position was considered, and the decision was made for WCB and EOP to retain the plus sign to align with ICH Q5D.
Comment Summary #156: The commenter suggested making edits to indicate that a Reverse Transcriptase (RT) Assay is to be performed if the TEM and Infectivity Assay are negative.
Response: Comment incorporated. Footnote was changed to "Not required if infectivity assay is positive." Footnote was moved from EOP to reverse transcriptase.
Comment Summary #157: The commenter suggested to revise Figure 4 and 5, Tables 3 and 4 to be more cohesive.
Response: Comment incorporated. Edits were made to Figures 4 and 5 to align with Tables 3 and 4.
Comment Summary #158: The commenter suggested adding references to USP chapters <63> *Mycoplasma Tests* and <71> *Sterility*.
Response: Comment not incorporated. The chapters are both referenced within the general chapter.
Comment Summary #159: The commenter requested to change the minus to a plus for WCB in the In Vitro Assay row of Table 4.
Response: Comment not incorporated. The table is aligned with ICH Q5A.
Comment Summary #160: The commenter suggested to remove RAP from footnote d in Figure 4.
Response: Comment incorporated. RAP was removed from footnote d in Figure 4.
Comment Summary #161: The commenter suggested to revise Bovine and porcine virus in vitro assay to include requirements for serum-free media.
Response: Comment incorporated. Bovine and porcine virus in vitro assay was revised to include requirements for serum-free media.
Comment Summary #162: The commenter suggested to change to plus sign for MCB for Identity Tests in Table 4.
Response: Comment incorporated. The minus sign was changed to a plus sign for the MCB for the Identity test in Table 4.
Comment Summary #163: The commenter suggested to remove RAP from footnote d, "Species-specific viruses present in rodent cell lines may be detected by mouse, rat, or hamster antibody production tests (MAP, RAP, or HAP)."
Response: Comment incorporated. RAP was removed from footnote d.
Comment Summary #164: The commenter suggested to add a reference to MMV and Vesivirus to footnote e of Table 4.
Response: Comment incorporated. References to MMV and Vesivirus were added to footnote e in Table 4.
Comment Summary #165: The commenter suggested to change MCB to a plus sign for Reverse transcriptase assay.
Response: Comment incorporated. A plus sign was added for the MCB for the Reverse transcriptase assay.
Comment Summary #166: The commenter suggested to add a footnote "Bovine and porcine virus in vitro Assay can be omitted for MCB, WCB and EOP if parental cell line used to generate

MCB had been tested negative for Bovine and porcine viruses and no animal-derived raw material were used in transfection and subsequent steps leading to the generation of MCB and WCB as well as in the production of EOP". If bovine and porcine raw materials were used but they have been sterilized by heat treatment or other means, there is no need to perform Bovine and porcine virus assay as well.
Response: Comment incorporated. A footnote was added that Bovine and porcine virus in vitro assay can be omitted for MCB, WCB and EOP if the parental cell line used to generate the MCB had tested negative for Bovine and porcine viruses, and no animal-derived raw material was used the steps to produce the EOP.
Comment Summary #167: The commenter suggested that Table 4 align with the new revision of ICH Q5A.
Response: Comment partially incorporated. ICH Q5A will not be revised and official for some time, so a footnote was added that states: For more information see current version of ICHQ5A. ICHQ5A is under revision during development of this chapter. The table is aligned with the current R1 version of ICH Q5A.
Comment Summary #168: The commenter suggested to move footnote "a" to the "In vitro assay" and to move footnote "b" to Adventitious Virus Detection in Table 4**.**
Response: Comment incorporated. Footnote a was removed from "In vitro Assay" and footnote b was moved to Adventitious Virus Detection in Table 4.
Comment Summary #169: The commenter suggested to specify that Bovine and porcine virus testing should only be required if materials of animal origin have been used in the cell line development or cell banking process. If no materials of animal origin are used, testing for these viruses should not be necessary**.**
Response: Comment incorporated. Text was added to clarify that Bovine and porcine virus testing is only required if materials of animal origin have been used in the cell line development.
Comment Summary #170: The commenter requested that minus sign be added to the "WCB" column for "infectivity" and "reverse transcriptase". The commenter suggested that there should be a plus sign for the MCB for the Reverse transcriptase assay.
Response: Comment incorporated. A minus sign was added to the WCB column for infectivity and reverse transcriptase. A plus sign was added to the MCB for the Reverse transcriptase Assay.
Comment Summary #171: The commenter suggested to remove "to confirm species identity".
Response: Comment not incorporated. It is necessary to confirm the cell line identity. Protein identity is characterized as part of the control strategy (coding sequence confirmation).

5.4 GENERAL CONSIDERATIONS FOR QUALIFICATION OF REPLACEMENT WCBS

Comment Summary #172: The commenter suggested the following edited text: "There is an option to use scale-down cell culture evaluation criteria including cell culture process key performance indicators (KPIs).
Response: Comment not incorporated. It is expected to do at least one full scale evaluation. Small scale data can be supportive in nature.

5.5 OTHER GENERAL CONSIDERATIONS FOR CELL BANKS

Comment Summary #173: The commenter requested to add considerations for vial tracking such as the need for tracking the number of vials made, the number of vials used and the number of vials remaining.
Response: Comment not incorporated. Tracking vial # is a business practice but is not needed to assess the quality of the cell bank.

Comment Summary #174: The commenter recommended rewording the following statement; "Each cell bank vial or bag should be labeled with **the appropriate information (e.g., identity, lot number, and date of freezing)** on liquid nitrogen-resistant cryolabels;"
Response: Comment partially incorporated. The statement was changed to align with response to another comment [Sec 3.2: "Label the vials in advance with the appropriate information (e.g., cell bank lot number, tube number, and production date)."]
Comment Summary #175: The commenter suggested the following edits for clarification: "post-bank thaw testing with assessment of cell viability should be performed **to demonstrate that the cells survived the cryopreservation process**."
Response: Comment partially incorporated. Suggested text changed to below to replace current text, "Post-bank thaw testing with assessment of cell viability should be performed **and documented. A viability limit should be set and justified to demonstrate that the cells survived the cryopreservation process. The viability limit could be set based on historical data.**"
Comment Summary #176: The commenter recommended shifting the focus from specific growth rate to cell bank viability as a parameter for cell bank stability.
Response: Comment incorporated. Discussion of specific growth rate was removed.
Comment Summary #177: The commenter suggested to change "freeze-thaw" to "thaw in the Cell Bank Storage Stability and Monitoring sub-section of 5.5 Other General Considerations for Cell Banks".
Response: Comment incorporated. "Freeze-thaw" was changed to "thaw."
Comment Summary #178: The commenter recommended deleting this sentence: "Limits should be updated as additional freeze-thaw data become available."
Response: Comment incorporated. The sentence was deleted.
Comment Summary #179: The commenter suggested to change the word "must" to "should" to allow for flexibility in this statement, "Data for WCB stability monitoring **must** include data from." The commenter indicated that for microbial cell banks, viability may not be determined during production of clinical or commercial material. Changing "must" to "should" will address this.
Response: Comment incorporated. The word "must" was changed to "should."
Comment Summary #180: The commenter indicated that it is relevant to not only look at statistical trends but also process demands. The evaluation should be a mix of evaluation of trends and if the performance is fit for the intended use. A cell bank may be fit for the intended use although a slight trend for e.g., decreasing viability is present. Process demands are a business need not a quality aspect. Criteria would be developed based on experience with the product developed to meet business needs.
Response: Comment not incorporated. The commenter's position was considered; no requested change was specifically identified.
Comment Summary #181: The commenter suggested to clarify or delete this sentence: "Limits should be updated as additional freeze-thaw data become available."
Response: Comment incorporated. The sentence was deleted.
Comment Summary #182: The commenter suggested the following edits to the sentence: "Limits should be updated as additional freeze–thaw data become available" - "if relevant for the process."
Response: Comment not incorporated. The sentence was deleted.
Comment Summary #183: The commenter suggested the following edits, including adding a specific example: "Data for WCB stability monitoring must include data from when 1 or more vials of the cryopreserved WCB are thawed for: A clinical or commercial production campaign. Until WCB is used for a clinical or commercial production campaign, data from lab scale post banking evaluation can be used."

Response: Comment partially incorporated. The specific example that was suggested to be added may not be applicable in all situations, so it was not added to the chapter. The word “must” was changed to “can” to allow for more flexibility.
Comment Summary #184: The commenter requested clarification of the statement, "use appropriate purity controls and limits."
Response: Comment not incorporated. The phrase, "use appropriate purity controls and limits" was deleted from the general chapter to improve clarity.
Comment Summary #185: The commenter suggested to add verbiage to specify a time point for start of stability monitoring.
Response: Comment not incorporated. The general chapter is intended to allow flexibility for when stability monitoring should begin.

GLOSSARY

Comment Summary #186: The commenter suggested to add definitions for End of production (EOP) cells and LIVCA**.**
Response: Comment not incorporated. Definitions for EOP and LIVCA already exist in the Glossary.

REFERENCES

Comment Summary #187: The commenter requested to correct the authors for the citation. The authors should be Berting, Farcet, and Kreil.
Response: Comment incorporated. The author names were corrected.

Monographs

Monograph/Section(s): Acetyltriethyl Citrate/Organic Impurities
Expert Committee: Simple Excipients

EC-initiated Change #1: Preparation of standard solutions was changed from one standard solution containing three reference standards (USP Triethyl Aconitate RS, USP Triethyl Aconitate RS, and USP Acetyltriethyl Citrate RS) to three separate standard solutions each containing only one reference standard, due to the presence of a Z-isomer of triethyl aconitate in USP Triethyl Aconitate RS that coelutes with triethyl citrate and also due to potential presence of triethyl aconitate and triethyl citrate in acetyltriethyl citrate used as a reference standard. The *System suitability* and *Analysis* sections of the test were updated to reflect the use of separate standard solutions.
EC-initiated Change#2: In Table 2, triethyl aconitate with relative retention time of 0.93 was specified as triethyl (*E*)-prop-1-ene-1,2,3-tricarboxylate.

Monograph/Section(s): Albuterol Tablets/Organic Impurities
Expert Committee: Small Molecules 5
No. of Commenters: 1

Comment Summary #1: The commenter recommended removing the reporting threshold in the test for Organic Impurities as it will vary based on product-specific factors.
Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that the issue of the removal of reporting thresholds from monographs needs further stakeholder engagement. USP intends to conduct further stakeholder engagement.
Comment Summary #2: The commenter recommended revising the acceptance criterion for Levalbuterol related compound C for consistency with what has been approved.
Response: Comment incorporated. The acceptance criterion for Levalbuterol related compound C is widened from "NMT 0.15%" to "NMT 0.2%" consistent with the current approved criterion.
Comment summary #3: The commenter recommended adding a footnote to refer to ICH M7 guidelines for the Levalbuterol related compound D impurity, as it possesses a structural alert for mutagenicity.
Response: Comment not incorporated. The Expert Committee determined that the proposed acceptance criterion is consistent with what has been approved by the agency and will consider future revisions to the monograph upon receipt of additional supporting data.

Monograph/Section(s): Alginic Acid/Impurities
Expert Committee: Complex Excipients
No. of Commenters: 7

Comment Summary #1: The commenter suggested modifying the statement under *Standard stock solution* in the test for *Limt of Lead and Arsenic*. The statement was proposed to modify from" ...and 500 µL of lead" to" ...and 500 µL of a standard solution containing 1000 mg/L of lead".
Response: Comment incorporated. As per the suggestion, the statement was modified Th"...and 500 µL of lead" to "...and 500 µL of a standard solution containing 1000 mg/L of lead to provide additional clarity.
Comment Summary #2: Under *Emission wavelengths*, the commenter suggested to correct the wavelength of yttrium internal standard emission line from "371.030 nm" to "224.306 nm" since this is much closer to the elements being analyzed.
Response: Comment incorporated. As per the suggestion, the yttrium internal standard emission line was corrected from "371.030 nm" to "224.306 nm", since this is much closer to the elements being analyzed.
Comment Summary #3: Under *Analysis*, the commenter suggested removing the statement related to in-line addition of internal standard since it was already added manually.
Response: Comment incorporated. As per the suggestion, the statement related to the in-line addition of internal standard was removed since it was already added manually.
Comment Summary #4: The commenter requested the removal of the testing for lead and arsenic in alginates. The commenter quoted a USP 2016 stimuli article which states," Unless there is a known quality or safety related reason to maintain the specific elemental impurity limit(s) currently in place for selected components (drug substance and excipients), implementation of <232> renders the specific element chapters and limit tests in monographs as unnecessary". The commenter also confirmed that they are not aware of any specific risk of lead and arsenic in alginates that require any specific controls.
Response: Comment not incorporated. Comments related to the applicability of elemental impurity testing to alginate monographs were discussed by the Complex Excipients Expert Committee. The expert committee considered the fact that alginates are naturally derived materials. The committee confirmed that additional data will be required from different alginate manufacturers to decide on the outright removal of the elemental testing from alginate monographs. Any such decision, based on limited data, may risk the overall safety of the

material. The committee determined that it could compromise the ability of a public standard to control such materials in terms of quality and safety.
Comment Summary #5: The commenter recommended not to reduce the limit of lead from 10 ppm to 5 ppm. It stated that process and/or analytical capability should not be the basis for lowering elemental impurity limits in existing monographs. Using process capability to tighten existing monograph limits for elemental impurities directly conflicts with ICH Q3D, which states that limits should be based on patient safety.
Response: Comment incorporated. Specific comments related to the lowering of the elemental impurity limits were considered and discussed with the Complex Excipient Expert Committee. Based on all of the data provided, the Expert Committee decided to keep the limit for lead unchanged at 10 ppm.
Comment Summary #6: The commenter suggested USP not to implement lowering the limits for lead and arsenic to 5 µg/g. Rather, USP should remove specifications for lead and arsenic from this monograph. It also said that ICH Q3D already addresses the need for safety control for these elements in the finished drug products. The commenter quoted USP 2016 stimuli article which states, “Unless there is a known quality or safety related reason to maintain the specific elemental impurity limit(s) currently in place for selected components (drug substance and excipients), implementation of <232> renders the specific element chapters and limit tests in monographs as unnecessary”.
Response: Comment partially incorporated. Specific comments related to the lowering of the elemental impurity limits were considered and discussed with the Complex Excipient Expert Committee. Comments related to the applicability of elemental impurity testing to alginate monographs were discussed with the Complex Excipients Expert Committee. The expert committee considered the fact that alginates are naturally derived materials. The committee confirmed that additional data will be required from different alginate manufacturers to decide on the outright removal of the elemental testing from alginate monographs. Any such decision, based on limited data, may risk the overall safety of the material. The committee confirmed that it could compromise the ability of a public standard to control such materials in terms of quality and safety. Hence this suggestion from the stakeholder was not accepted.
Comment Summary #7: The commenter suggested developing Alginic acid as a flexible monograph with the option to use wet chemistry tests as an alternative, to determine elemental impurities such as lead and arsenic.
Response: Comment not incorporated. The Complex Excipients Expert Committee recommended keeping the elemental impurity testing for lead and arsenic based on ICP-OES. ICP-OES based procedure has been incorporated to accurately and precisely quantify the specific elemental impurities. The committee decided not to add an option to use wet chemistry tests for this purpose, because it would be contrary to the purpose of this revision.

Monograph/Section(s): Amphetamine Sulfate Tablets/Dissolution
Expert Committee: Small Molecules 4
No. of Commenters: 1

Comment Summary #1: The commenter requested to add a dissolution test which accommodates their approved drug product.
Response: Comment partially incorporated. The Expert Committee determined that the dissolution parameters and tolerance from the commenter are consistent or tighter than that published for Dissolution Test 2 except for the *Medium* which requires deaeration. The *Medium* in Dissolution Test 2 is updated from “Medium: water; 500 mL” to “Medium: water; 500mL, deaerated if necessary”.

Monograph/Section(s): Artemether/Organic Impurities
Expert Committee: Small Molecules 1
No. of Commenters: 1

Comment summary #1: The commenter recommended removing the reporting threshold as it will vary based on product-specific factors.
Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that the issue of the removal of reporting thresholds from monographs needs further stakeholder engagement. USP intends to conduct further stakeholder engagement.

Monograph/Section(s): Atomoxetine Hydrochloride/Organic Impurities
Expert Committee: Small Molecules 4
No. of Commenters: 1

Comment Summary #1: The commenter recommended removing the reporting threshold in the test for *Organic Impurities* as it will vary based on product-specific factors.
Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that the issue of the removal of reporting thresholds from monographs needs further stakeholder engagement. USP intends to conduct further stakeholder engagement.

Monograph/Section(s): Calcium Propionate/Multiple sections
Expert Committee: Simple Excipients

EC-initiated Change#1: A note of "The peak eluting at RRT 0.3 is the calcium ion peak. This peak and the peaks eluting before it is excluded from integration. These peaks are not from organic impurities of Calcium Propionate" was added in the *Analysis* section of the *Organic Impurities* test to offer clarity.
EC-initiated Change#2: "Plot the calibration curve versus potential, in mV, on two-cycle semilogarithmic paper with µg of fluoride per 100 mL of solution on the logarithmic scale" was changed to "Construct a calibration curve by plotting potential, in mV, versus logarithm of µg of fluoride per 100 mL of solution" in the *Limit of Fluoride* test to offer users more flexibility in constructing the calibration curve, and the footnote 1 was deleted in this test because this footnote, which contains a broken link to a semilogarithmic paper supplier, is not needed anymore with the change made for constructing the calibration curve.

Monograph/Section(s): Carboplatin Injection/Organic Impurities
Expert Committee: Small Molecules 3
No. of Commenters: 2

EC-initiated Change #1: Change from "Any individual unspecified degradation product" to "Any unspecified degradation product" in Table 1, to be consistent with ICH terminology.
Comment Summary #1: The commenters recommended revising the acceptance criteria for "Cyclobutane dicarboxylic acid" and "Total degradation products" to be consistent with what have been approved by the agency.
Response: Comment incorporated. The acceptance criteria for "Cyclobutane dicarboxylic acid" is revised from "NMT 0.4%" to "NMT 1.0%," and the limit for the "Total degradation products" is revised from "NMT 0.5%" to "NMT 2.5%." In addition, a footnote is added to "Total degradation products" in Table 1 to indicate that the amount of "Cyclobutane dicarboxylic acid" is included in the limit for "Total degradation products."

Comment Summary #2: The commenter recommended removing the reporting threshold from the test for Organic Impurities as it will vary based on product-specific factors.
Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that the issue of the removal of reporting thresholds from monographs needs further stakeholder engagement. USP intends to conduct further stakeholder engagement.

Monograph/Section(s): Carteolol Hydrochloride/Organic Impurities
Expert Committee: Small Molecules 2
No. of Commenters: 1

Comment summary #1: The commenter recommended removing the reporting threshold as it will vary based on product-specific factors.
Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that the issue of the removal of reporting thresholds from monographs needs further stakeholder engagement. USP intends to conduct further stakeholder engagement.

Monograph/Section(s): Chlorthalidone/Multiple Sections
Expert Committee: Small Molecules 2
No. of Commenters: 2

Comment Summary #1: The commenter recommended removing the reporting threshold from the *Organic Impurities* test as it will vary based on product-specific factors.
Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that the issue of the removal of reporting thresholds from monographs needs further stakeholder engagement. USP intends to conduct further stakeholder engagement.
Comment Summary #2: The commenter recommended harmonizing the *Assay* and *Organic Impurities* methods with the current EP monograph with regard to the injection volume and gradient program for both methods and the concentration of the *Standard solution* in the *Organic Impurities* method.
Response: Comment not incorporated. The *Assay* and *Organic Impurities* methods are based on the validated procedures and are suitable for the intended use. As appropriate, the Expert Committee will consider future revisions to this monograph upon receipt of supporting information.

Monograph/Section(s): Chlorthalidone Tablets/Multiple Sections
Expert Committee: Small Molecules 2
No. of Commenters: 2

Comment Summary #1: The commenter recommended removing the reporting threshold from the *Organic Impurities* test as it will vary based on product-specific factors.
Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that the issue of the removal of reporting thresholds from monographs needs further stakeholder engagement. USP intends to conduct further stakeholder engagement.
Comment Summary #2: The commenter indicated that they utilize the EP Chlorthalidone System Suitability CRS in the preparation of the *System Suitability Solution* for peak identification in their organic impurities test.

Response: Comment not incorporated. USP Reference Standards that have been qualified as suitable for use are provided for the analysis.
Comment Summary #3: The commenter indicated that the concentration (1 µg/mL) for the *Sensitivity Solution* in the *Organic Impurities* test differs from their LOQ concentration (0.5 µg/mL).
Response: Comment not incorporated. The concentration of the *Sensitivity solution* at 0.1% level is consistent with the reporting threshold and is suitable for the *Organic Impurities* test.
Comment Summary #4: The commenter indicated that the proposed *Organic Impurities* method includes the signal-to-noise ratio requirement based on the *Sensitivity solution*, whereas their method does not include a signal to noise ratio requirement.
Response: Comment not incorporated. The Expert Committee determined that the signal-to-noise ratio requirement is important in controlling the system sensitivity for a public standard.
Comment Summary #5: The commenter indicated that the RRT for Chlorthalidone EP Impurity J is 0.95 in their *Organic Impurity* method, but 1.1 in the proposed *Organic Impurities* method.
Response: Comment not incorporated. The RRT value of 1.1 is consistent with the supporting data.
Comment Summary #6: The commenter indicated their method also accounts for the RRT values of other impurities (CPSP and Chlorthalidone EP Impurity G), whereas the proposed USP *Organic Impurities* method does not establish RRT values for these compounds.
Response: Comment not incorporated. These are not specified impurities in the commenter's approved specification but are controlled under the any unspecified impurity at NMT 0.2%.
Comment Summary #7: The commenter recommended revising the sonication time from NLT 15 minutes to NLT 10 minutes for *Sample stock solution* in the *Assay* test and *Sample solution* in the *Organic Impurities* test.
Response: Comment incorporated. The sonication time was moved to the *Note* and revised to "NLT 10 minutes" to provide flexibility and accommodate different formulations.
Comment Summary #8: The commenter recommended removing the *Tailing factor* requirement of "NMT 2.0" from the *Assay* test as this system suitability requirement is not explicitly stated in their method.
Response: Comment not incorporated. The Expert Committee determined that the tailing factor requirement of NMT 2.0 is suitable to be included in the *Assay* test based on the supporting data.

Monograph/Section(s): Curcuminoids Capsules/Identification, Performance Tests
Expert Committee: Botanical Dietary Supplements and Herbal Medicines
No. of Commenters: 1

EC-initiated Change #1: The Expert Committee changed the description of the HPTLC data for *Identification A* to be corrected to reflect HPTLC data for curcuminoids rather than turmeric rhizome (Curcuma longa).
EC-initiated Change #2: The Expert Committee added an explanation to the statement "making any necessary modification" in the *Analysis* under *Disintegration and Dissolution* for further clarity.

Monograph/Section(s): Curcuminoids Tablets/Identification, Performance Tests
Expert Committee: Botanical Dietary Supplements and Herbal Medicines
No. of Commenters: 1

EC-initiated Change #1: The Expert Committee made a modification in *Identification A t*o follow the recommendations provided to the Curcuminoids Capsules monograph.

EC-initiated Change #2: To provide additional clarity, the Expert Committee made a modification to use the same clarification wording as in is used in the *Disintegration and Dissolution* section of the Curcuminoids Capsules monograph.

Monograph/Section(s): Cyclophosphamide Capsules/Multiple sections
Expert Committee: Small Molecules 3
No. of Commenters: 2

EC-initiated Change #1: The EC revised the resolution requirement between cyclophosphamide related compound A and cyclophosphamide peaks in the test for *Organic Impurities* from “NLT 5.0” to “NLT 3.0” based on supporting data.
Comment summary #1: The commenter recommended removing the reporting threshold from the test for *Organic Impurities* as it will vary based on product-specific factors.
Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that the issue of the removal of reporting thresholds from monographs needs further stakeholder engagement. USP intends to conduct further stakeholder engagement.
Comment summary #2: The commenter requested their *Assay* be used in the monograph.
Response: Comment not incorporated. The EC determined that the requested changes provide no major benefit over the published proposal.
Comment summary #3: The commenter requested changing the *Autosampler temperature* from 4° to ambient in Assay.
Response: Comment not incorporated. The *Autosampler temperature* was proposed based on a validated method of analysis. The EC will consider future revision to the monograph upon the receipt of necessary supporting data.
Comment summary #4: The commenter requested their *Dissolution* procedure for Tier 2 be used in the monograph.
Response: Comment not incorporated. The request is accounted for in the statement included in the published proposal indicating that it is permissible to use *Dissolution ⟨711⟩, For Dosage Forms Containing or Coated with Gelatin* as an alternative procedure.

Monograph/Section(s): Dextrates/Multiple sections
Expert Committee: Complex Excipients
No. of Commenters: 1

EC-initiated Change#1: In the *Definition* and the *Assay*, retain the upper limit of NMT 99.0%. A product with a DE greater than 99.0% would be "dextrates" rather than just simply "dextrose”.
EC-initiated Change#2: The EC changed title of “USP Hydrated Dextrates RS” to “Dextrates Monohydrate RS” to be consistent with naming of USP RS. The incorporated title change is also consistent with the supporting data, which describes the material as monohydrate (hydrate containing single molecule of water of crystallization per molecule) and is therefore more specific.
EC-initiated Change#3: In the *Identification B test*, the upper limit of *Melting range or temperature* was relaxed from 144° to 146°. The melting point for dextrose is 146° which is in alignment with assay data (the dextrose equivalence (assay) for bulk lot is 99%) and melting point data was received, so an upper limit of 144° may not be inclusive of a highly hydrolyzed product.
EC-initiated Change#4: In the *Definition* and *Assay*, the phrase ‘on dried basis’ was removed to address a problem with calculation. The *Assay* calculation originally is based on %TDA.
Comment Summary #1: Commenter suggested to change column and detector temperatures, as their HPLC column and detector temperatures are not calibrated to ±1 °C as proposed.

Response: Comment incorporated. Variance (±1 °C) associated with column and detector temperatures are adjusted to a note because these details are informative that help to achieve system suitability requirements.

Monograph/Section(s): Dextrose and Sodium Chloride Injection/Assay
Expert Committee: Small Molecules 5
No. of Commenters: 1

Comment Summary #1: The commenter recommended removing the new *Sample solution for products that are terminally sterilized* because they stated that it is not suitable for products containing higher strengths of dextrose.
Response: Comment incorporated. The new *Sample solution for products that are terminally sterilized* in the *Assay* was removed and a *Note* was added to the original *Sample solution* stating that "ammonium hydroxide may be omitted for finished products containing up to 10% dextrose that have been terminally heat sterilized".

Monograph/Section(s): Dutasteride and Tamsulosin Hydrochloride Capsules/Organic Impurities
Expert Committee: Small Molecules 3
No. of Commenters: 2

Comment summary #1: The commenter recommended removing the reporting threshold as it will vary based on product-specific factors.
Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that the issue of the removal of reporting thresholds from monographs needs further stakeholder engagement. USP intends to conduct further stakeholder engagement.
Comment summary #2: Commenter recommended revising the acceptance criteria for "any unspecified degradation product" associated with dutasteride and tamsulosin hydrochloride to align with what has been approved by the agency, and to be consistent with the identification threshold as per ICH-Q3B.
Response: Comment incorporated. Based on specifications obtained from a manufacturer with an FDA approved drug product application, the acceptance criteria for "any unspecified degradation product" for Dutasteride and Tamsulosin hydrochloride are each revised to NMT 1.0%.
Comment summary #3: The commenter requested to revise the acceptance criteria for the "total degradation products" of tamsulosin hydrochloride to be consistent with what has been approved by the agency.
Response: Comment incorporated. Based on specifications obtained from a manufacturer with an FDA approved drug product application, the acceptance criteria for "total degradation products" associated with tamsulosin hydrochloride is increased to NMT 1.0%.
Comment summary #4: The commenter recommended removing chlorodutasteride from the list of specified impurities as it may be sufficiently controlled in the drug substance.
Response: Comment incorporated. Removed chlorodutasteride as a specified impurity controlling it under any unspecified degradation product acceptance criteria.
Comment summary #5: The commenter recommended removing the list of process impurities in the acceptance criteria Table 3 and Table 5 because the agency is unable to confirm whether these impurities are process-only for all approved products.
Response: Comment incorporated. The process impurities listed in Tables 3 and 5 did not have any associated acceptance criteria and the relative retention times were provided for information. No other identified impurities with associated acceptance criteria remain.

Therefore, tables 3 and 5 listing the process impurities with associated relative retention times are removed. The *Acceptance criteria* section maintains the limits for “any unspecified degradation product” and “total degradation products.”
Comment summary #6: The commenter requested a consistent designation on whether dutasteride acid is a process impurity or degradation product across the two dutasteride-containing drug product monograph proposals published in PF 46(5). The commenter requested the removal of the impurity if designated as a process impurity.
Response: Comment incorporated. See the response to comment #5. Tables 3 and 5 listing the process impurities with associated relative retention times are removed. The *Acceptance criteria* section maintains the limits for “any unspecified degradation product” and “total degradation products.”

Monograph/Section(s): Emtricitabine/Multiple sections
Expert Committee: Small Molecules 1
No. of Commenters: 3

EC-Initiated Change #1: The EC changed “Any individual unspecified impurity” to “Any unspecified impurity” in Table 2 of the *Organic Impurities* section to be consistent with ICH terminology.
EC-Initiated Change #2: The EC updated the descriptions for the USP Emtricitabine System Suitability Mixture A RS and USP Emtricitabine System Suitability Mixture B in the USP Reference Standards <11> section to be consistent with the current USP practice.
Comment Summary #1: The commenter indicated that the following impurities have different limits from those in agency-approved products: Emtricitabine acid; Emtricitabine *S*-sulfoxide; Emtricitabine *R*-sulfoxide; Lamivudine; Emtricitabine 5-fluorouracil analog; Emtricitabine enantiomer; Emtricitabine 5-epimer; and Emtricitabine 2-epimer.
Response: Comment partially incorporated. The *Acceptance criteria* were widened from “0.15%” to “0.50%” for Emtricitabine acid and from “0.15%” to “0.20%” for Lamivudine, consistent with data provided The Expert Committee will consider future revisions to this monograph upon receipt of supporting information.
Comment Summary #2: The commenter requested to widen the limits for the Emtricitabine *S*-sulfoxide impurity.
Response: Comment not incorporated. The Expert Committee will consider future revisions to this monograph upon receipt of supporting information.
Comment Summary #3: The commenter requested to include 197A for *Identification* A.
Response: Comment not incorporated. The Expert Committee will consider future revisions to this monograph upon receipt of supporting information.
Comment Summary #4: The commenter requested relaxing the *System suitability requirement* for *Relative standard deviation* for the *Assay* test to “NMT 2.0%” from the proposed “NMT 0.73%”.
Response: Comment not incorporated. A relative standard deviation of “NMT 0.73%” is current USP practice and in line with General Chapter <621>.
Comment Summary #5: The commenter requested relaxing the limit for *Residue on Ignition* from the proposed “NMT 0.10%” to “NMT 0.1%” based on their FDA-approved limit.
Response: Comment incorporated. The limit for ROI has been revised from NMT 0.10% to NMT 0.1%.
Comment Summary #7: The commenter requested to add additional impurities (FTC-Dioxolane and FTC-Disulfide) with limits to the monograph.
Response: Comment not incorporated. The Expert Committee will consider future revisions to this monograph upon receipt of supporting information.

Comment Summary #8: The commenter requested removing the Lamivudine impurity from the monograph, as it is not included in their FDA-approved specifications.
Response: Comment not incorporated. The impurity is consistent with known FDA-approved product specifications.

Monograph/Section(s): Fosamprenair Calcium Tablets/Multiple sections
Expert Committee: Small Molecules 1
No. of Commenters: 4

EC-initiated Change #1: The EC changed "Any individual unspecified impurity" to "Any unspecified impurity" in Table 1 of the *Organic Impurities: Early-Eluting Impurities* section and in Table 3 of the *Organic Impurities: Late-Eluting Impurities* section to be consistent with ICH terminology.
EC-initiated Change #2: The EC removed the Relative response factor (*F*) for all impurities in Table 1 of the *Organic Impurities: Early-Eluting Impurities* section and in Table 3 of the *Organic Impurities: Late-Eluting Impurities* section. In addition, as the Relative response factor is not needed, the "(1/*F*)" from the equations and corresponding definitions are removed.
EC-initiated Change #3: The EC update the description for the USP Fosamprenavir Calcium System Suitability Mixture RS to be consistent with what is listed in the API monograph.
EC-initiated Change #4: The EC changed the nominal concentration for *Sample solutions* prepared throughout the proposed monograph based on the labeled amount of fosamprenavir as opposed to the fosamprenavir calcium.
Comment Summary #1: The commenter indicated that the concentration of the *Standard solution* in the *Dissolution* test is incorrect as it should be "0.78 mg/mL of fosamprenvir" as opposed to "0.78 mg/mL of fosamprenavir calcium."
Response: Comment incorporated. The *Standard solution* preparation is changed to "0.83 mg/mL" of USP Fosamprenavir Calcium RS, which is equivalent to 0.78 mg/mL of fosamprenavir. In addition, as there is no dilution of the *Sample solution*, the "*D*" from the *Dissolution* equation and corresponding definition is removed.
Comment Summary #2: The commenter indicated that the *Dissolution* acceptance criteria are different from those in agency-approved products.
Response: Comment not incorporated. The acceptance criteria are based on known approved specifications. The Expert Committee will consider future revisions to this monograph upon receipt of supporting information.
Comment Summary #3: The commenter recommended removing the reporting threshold as it will vary based on product-specific factors.
Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that the issue of the removal of reporting thresholds from monographs needs further stakeholder engagement. USP intends to conduct further stakeholder engagement.
Comment Summary #4: The commenter requested UV cuvette length information be added to the *Dissolution* test as, when using the default 1 cm path length cell, the instrument is saturated at the 0.78 mg/mL concentration of the *Standard solution*.
Response: Comment incorporated. The path length of a 0.02 cm cell is consistent with the sponsor's method and avoids the instrument being saturated. Therefore, the path length of a 0.02 cm cell is added to the proposed monograph.

Monograph/Section(s): Hydrogenated Polydextrose/Specific tests, Assay
Expert Committee: Complex Excipients
No. of Commenters: 3

Comment Summary #1: The commenter suggested to incorporate a note 'Temperature can be adjusted depending on titrator's capability'. This change was suggested under the water determination test, wherein drift was not getting stabilized at procedure recommended temperature of 50C. Analysis at 42 C resolved the issue since the drift stabilized below 20 µg/min.
Response: Comment incorporated. As per the stakeholder's suggestion a note has been added 'Temperature can be adjusted depending on titrator's capability.' This temperature change will help control the instrument drift.
Comment Summary #2: The commenter suggested to incorporate a note 'Molecular weights for the standards can be selected as available commercially, while maintaining the required calibration range'. This change was suggested under the test molecular weight limit. Since the use of any of the commercially available standards for the calibration curve does not affect the final calibration and the results if the standards selected are within the recommended calibration range.
Response: Comment incorporated. As per the stakeholder's suggestion, a note has been added 'Molecular weights for the standards can be selected as available commercially, while maintaining the required calibration range.' This will not have any impact on the calibration curve as well as the end results.
Comment Summary #3: The commenter suggested removing the details about sensitivity for RI detector under molecular weight limit. The current value of setting a sensitivity of 4×10^{-6} refractive index units full scale is too specific and mandates the use of specific make of refractive index detector. Removing this instrument specific requirement will not have any impact on the sensitivity of the detector and in turn the end results.
Response: Comment incorporated. As per the stakeholder's suggestion, details about the sensitivity of the RI detector were deleted as this becomes an instrument specific instruction.
Comment Summary #4: The commenter suggested checking on the inclusion of peaks eluted at the tailing of the main peak (before dextrose) as a part of the main peak as hydrogenated polydextrose. It also suggested including a note specifying how to integrate the main peak for the assay.
Response: Comment incorporated. The Expert Committee determined that the peaks eluting at the tailing of the main peak as shorter chain polymers and to be included as a part of the main peak of hydrogenated polydextrose. A note stating, 'Integrate and include smaller peaks eluted on the tailing of the Hydrogenated Polydextrose to be included as a part of assay' was incorporated in the assay section of the monograph under analysis.

Monograph/Section(s): Linezolid Tablets/Organic Impurities
Expert Committee: Small Molecules 1
No. of Commenters: 1

Comment Summary #1: The commenter requested removing the reporting threshold as it will vary based on product-specific factors. The commenter also commented that the proposed reporting threshold at 0.005% is much lower than the ICH reporting threshold.
Response: Comment partially incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that the issue of the removal of reporting thresholds from monographs needs further stakeholder engagement. USP intends to conduct further stakeholder engagement. The reporting threshold was widened from 0.005% to 0.05% to be in line with ICH guidelines and the sensitivity solution concentration was increased from 0.05 ug/mL to 0.5 ug/mL to be in line with the Reporting threshold level.
Comment Summary #2: The commenter indicated that acceptance criterion for any individual unspecified impurity should be consistent with ICH Q3B guidelines and the acceptance criterion for Linezolid related compound C is different from what has been approved by the FDA.

Response: Comment incorporated. The acceptance criteria were widened from “NMT 0.15%” to “NMT 0.17%” for any individual unspecified impurity and from “NMT 0.20%” to “NMT 0.2%” for Linezolid related compound C, consistent with data provided.
Comment Summary #3: The commenter indicated that impurity profile is missing degradation products.
Response: Comment not incorporated. The Expert Committee will consider future revisions to this monograph upon receipt of the necessary supporting data.

Monograph/Section(s): Maltodextrin/Identification
Expert Committee: Complex Excipients
No. of Commenters: 2

Comment Summary #1: Commenters suggested identification by Infrared Spectrometry in lieu of the identity by Dextrose Equivalent (titrimetry). As the current *Assay* is not an ideal identification test, other polysaccharides could react with the cupric tartrate titrant, possibly generating false positive results.
Response: Comment not incorporated. Comments on this topic may be addressed through a future *Forum* proposal based on supporting data.

Monograph/Section(s): Meclofenamate Sodium**/**Multiple Sections
Expert Committee: Small Molecules 2
No. of Commenters: 1

Comment Summary #1: The commenter recommended tightening the Acceptance criteria for the *Assay* from “97.0%-103.0%” to “98.0%–102.0%”.
Response: Comment not incorporated. The *Acceptance criteria* of 97.0%–103.0%, which remain unchanged in the proposed proposal, are consistent with what have been approved by the FDA. The Expert Committee will consider future revisions to the monograph upon receipt of supporting data, as appropriate.
Comment Summary #2: The commenter requested removing the reporting threshold from the *Organic Impurities* test as it will vary based on product-specific factors.
Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that the issue of the removal of reporting thresholds from monographs needs further stakeholder engagement. USP intends to conduct further stakeholder engagement

Monograph/Section(s): Pamidronate Disodium for Injection/Assay
Expert Committee: Small Molecules 3
No. of Commenters: 1

Comment summary #1: The commenter recommended including a temperature control for the refractive index detector at the same temperature as the column and adding a note that the system should be equilibrated until stable base line is obtained.
Response: Comment not incorporated. The comment is outside the scope of the proposed revisions. The EC will consider future revisions to the monograph upon receipt of the necessary supporting data.

Monograph/Section(s): Polyvinyl Alcohol/Definition
Expert Committee: Complex Excipients
No. of Commenters: 1

Comment Summary #1: The commenter enquired about an update in the chemical formula to specify that the material is partially hydrolyzed. But there is no such statement in the definition section to indicate the material is partially hydrolyzed.
Response: Comment not incorporated. The degree of hydrolysis with 85-89% included in the definition section itself indicates, that the current monograph represents partially hydrolyzed polyvinyl acetate (to polyvinyl alcohol).

Monograph/Section(s): Potassium Alginate/Impurities
Expert Committee: Complex Excipients
No. of Commenters: 6

Comment Summary #1: The commenter suggested modifying the statement under Standard stock solution. The statement was proposed to modify from" ...and 500 µL of lead" to "...and 500 µL of a standard solution containing 1000 mg/L of lead".
Response: Comment incorporated. As per the suggestion, the statement was modified from "...and 500 µL of lead" to "...and 500 µL of a standard solution containing 1000 mg/L of lead" for clarity.
Comment Summary #2: Under Emission wavelengths, the commenter suggested to correct wavelength of yttrium internal standard emission line from "371.030 nm" to "224.306 nm" because this is much closer to the elements being analyzed.
Response: Comment incorporated. As per the suggestion, the yttrium internal standard emission line was corrected from "371.030 nm" to "224.306 nm", since this is much closer to the elements being analyzed.
Comment Summary #3: Under the *Analysis*, the commenter suggested removing the statement related to the in-line addition of the *Internal standard solution* since it was already added manually.
Response: Comment incorporated. As per the suggestion, the statement related to the in-line addition of the *Internal standard solution* was removed since it was already added manually.
Comment Summary #4: The commenter quoted a USP 2016 *Stimuli* article which states," Unless there is a known quality or safety related reason to maintain the specific elemental impurity limit(s) currently in place for selected components (drug substance and excipients), implementation of <232> renders the specific element chapters and limit tests in monographs as unnecessary". The commenter also confirmed that they are not aware of any specific risk of lead and arsenic in alginates that require any specific controls.
Response: Comment not incorporated. Comments related to the applicability of elemental impurity testing of alginate monographs were discussed by the Complex Excipients Expert Committee. The Expert Committee considered the fact that alginates are naturally derived materials. The committee confirmed that additional data will be required from different alginate manufacturers to decide on the outright removal of the elemental testing from alginate monographs. Any such decision, based on the limited data, may risk the overall safety of the material. The committee determined that it could compromise the ability of a public standard to control such materials in terms of quality and safety.
Comment Summary #5: The commenter recommended not to reduce the limit of lead from 10 ppm to 5 ppm. It stated that process and/or analytical capability should not be the basis for lowering elemental impurity limits in existing monographs. Using process capability to tighten existing monograph limits for elemental impurities directly conflicts with ICH Q3D, which states that limits should be based on patient safety.
Response: Comment incorporated. Comments related to the lowering of the elemental impurity limits were considered and discussed with the Complex Excipient Expert Committee. As per the committee's recommendations, the limit for lead was kept unchanged at 10 ppm.

Comment Summary #6: The commenter suggested USP not implement lowering the limit of lead to 5 µg/g. Rather, USP should remove specifications for lead and arsenic from this monograph. It also said that ICH Q3D already addresses the need for safety control for these elements in the finished drug products. The commenter quoted USP 2016 *Stimuli* article which states, “Unless there is a known quality or safety related reason to maintain the specific elemental impurity limit(s) currently in place for selected components (drug substance and excipients), implementation of <232> renders the specific element chapters and limit tests in monographs as unnecessary”.
Response: Comment partially incorporated. Comments related to the lowering of the elemental impurity limits were considered and discussed with the Complex Excipient Expert Committee. As per the committee’s recommendations, the limit for lead was kept unchanged at 10 ppm.

Comments related to the applicability of elemental impurity testing of alginate monographs were discussed by the Complex Excipients Expert Committee. The Expert Committee considered the fact that alginates are naturally derived materials. The committee confirmed that additional data will be required from different alginate manufacturers to decide on the outright removal of the elemental testing from alginate monographs. Any such decision, based on the limited data, may risk the overall safety of the material. The committee determined that it could compromise the ability of a public standard to control such materials in terms of quality and safety

Monograph/Section(s): Quinapril and Hydrochlorothiazide Tablets **/**Multiple Sections
Expert Committee: Small Molecules 2
No. of Commenters: 1

EC-initiated Change #1: The phrase "of the labeled amount" was added to the calculation descriptions within the *Assay* and the test for *Dissolution* for clarity and consistency with current USP style.
Comment Summary #1: The commenter requested removing the reporting threshold from the *Organic Impurities* test as it will vary based on product-specific factors.
Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that the issue of the removal of reporting thresholds from monographs needs further stakeholder engagement. USP intends to conduct further stakeholder engagement.
Comment Summary #2: The commenter requested removing process impurities without acceptance criteria from the Table 5 in the *Organic impurities* test. Those include Chlorothiazide, 5-Chlorohydrochlorothiazide, Hydrochlorothiazide dimer, Quinapril methyl ester, Quinapril isopropyl ester, Hexahydroquinapril, and Quinapril benzyl ester.
Response: Comment not incorporated. Removing process impurity is outside the scope of this revision. The Expert Committee may consider future revisions to the monograph upon the receipt of supporting data.

Monograph/Section(s): Risedronate Sodium Delayed-Release Tablets/Multiple sections
Expert Committee: Small Molecules 3
No. of Commenters: 2

Comment summary #1: The commenter recommended removing the reporting threshold from the test for *Organic Impurities* as it will vary based on product-specific factors.
Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that the issue of the removal of reporting thresholds from monographs needs further stakeholder engagement. USP intends to conduct further stakeholder engagement.

Comment summary #2: The commenter recommended lowering the *Standard solution* concentration and revising the acceptance criteria for relative standard deviation accordingly in the test for *Organic Impurities* to ensure the system precision at impurity quantification level.
Response: Comment not incorporated. The *Standard solution* concentration of 0.1 mg/mL is supported by validation data with linearity and accuracy data which covers the unspecified impurity limit of NMT 0.2%.
Comment summary #3: The commenter requested to replace the *Assay* and the *Organic Impurities* test with their methods, as the commenter found that non-metallic HPLC systems are not available in the market.
Response: Comment not incorporated. The EC decided to remove the note in the proposal stating "[NOTE—Use a non-metallic liquid chromatography system for analysis.]" to avoid possible confusion.

Monograph/Section(s): Rivaroxaban Tablets/Multiple Sections
Expert Committee: Small Molecules 2
No. of Commenters: 2

Comment Summary #1: The commenter recommended removing the reporting threshold from the test for *Organic Impurities* as it will vary based on product-specific factors.
Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that the issue of the removal of reporting thresholds from monographs needs further stakeholder engagement. USP intends to conduct further stakeholder engagement.
Comment Summary #2: The commenter requested modifying the preparation of the *Standard stock solution* within the test for *Dissolution* as they observed that rivaroxaban was not soluble.
Response: Comment not incorporated. The expert committee has determined that the solution preparation as written is suitable for inclusion in the public standard.

Monograph/Section(s): Sodium Alginate/Impurities, Assay
Expert Committee: Complex Excipients
No. of Commenters: 7

Comment Summary #1: The commenter suggested modifying the statement under Standard stock solution. The statement was proposed to modify from "...and 500 µL of lead" to "...and 500 µL of a standard solution containing 1000 mg/L of lead".
Response: Comment incorporated to modify "...and 500 µL of lead" to "...and 500 µL of a standard solution containing 1000 mg/L of lead" for clarity.
Comment Summary #2: Under *Emission wavelengths*, the commenter suggested to correct the wavelength of yttrium internal standard emission line from "371.030 nm" to "224.306" nm since this is much closer to the elements being analyzed.
Response: Comment incorporated to correct the internal standard emission line from "371.030 nm" to "224.306 nm." This wavelength is much closer to the elements being analyzed.
Comment Summary #3: Under the *Analysis*, the commenter suggested removing the statement related to in-line addition of internal standard since it was already added manually.
Response: Comment incorporated to remove the statement related to the in-line addition of internal standard. The internal standard is already being added manually.
Comment Summary #4: In the *Assay* section of the Sodium Alginate monograph, the commenter highlighted a typographical error which needed to be corrected from "Transfer the filter crucible to a beaker" to "Transfer the contents of the filter crucible to a beaker".
Response: Comment incorporated to correct a typographical error from "Transfer the filter crucible to a beaker" to "Transfer the contents of the filter crucible to a beaker".

Comment Summary #5: The commenter quoted a USP 2016 *Stimuli* article which states, ”Unless there is a known quality or safety related reason to maintain the specific elemental impurity limit(s) currently in place for selected components (drug substance and excipients), implementation of <232> renders the specific element chapters and limit tests in monographs as unnecessary”. The commenter also confirmed that they are not aware of any specific risk of lead and arsenic in alginates that require any specific controls.
Response: Comment not incorporated. Comments related to the applicability of elemental impurity testing of alginate monographs were discussed by the Complex Excipients Expert Committee. The Expert Committee considered the fact that alginates are naturally derived materials. The committee confirmed that additional data will be required from different alginate manufacturers to decide on the outright removal of the elemental testing from alginate monographs. Any such decision, based on the limited data, may risk the overall safety of the material. The committee determined that it could compromise the ability of a public standard to control such materials in terms of quality and safety
Comment Summary #6: The commenter recommended not to reduce the limit of lead from 10 ppm to 5 ppm. It stated that process and/or analytical capability should not be the basis for lowering elemental impurity limits in existing monographs. Using process capability to tighten existing monograph limits for elemental impurities directly conflicts with ICH Q3D, which states that limits should be based on patient safety.
Response: Comment incorporated. Specific comments related to the lowering of the elemental impurity limits were considered and discussed with the Complex Excipient Expert Committee. Comments related to the applicability of elemental impurity testing to alginate monographs were discussed by the Complex Excipients Expert Committee. The expert committee considered the fact that alginates are naturally derived materials. The committee confirmed that additional data will be required from different alginate manufacturers to decide on the outright removal of the elemental testing from alginate monographs. Any such decision, based on limited data, may risk the overall safety of the material. The committee determined that it could compromise the ability of a public standard to control such materials in terms of quality and safety.
Comment Summary #7: The commenter suggested USP not implement lowering the limit to 5 µg/g. Rather, USP should remove specifications for lead and arsenic from this monograph. It also said that ICH Q3D already addresses the need for safety control for these elements in the finished drug products. The commenter quoted USP 2016 *Stimuli* article which states, ”Unless there is a known quality or safety related reason to maintain the specific elemental impurity limit(s) currently in place for selected components (drug substance and excipients), implementation of <232> renders the specific element chapters and limit tests in monographs as unnecessary”.
Response: Comment partially incorporated. Comments related to the lowering of the elemental impurity limits were considered and discussed with the Complex Excipient Expert Committee. As per the committee’s recommendations, the limit for lead was kept unchanged at 10 ppm.

Comments related to the applicability of elemental impurity testing to alginate monographs were discussed by the Complex Excipients Expert Committee. The expert committee considered the fact that alginates are naturally derived materials. The committee confirmed that additional data will be required from different alginate manufacturers to decide on the outright removal of the elemental testing from alginate monographs. Any such decision, based on limited data, may risk the overall safety of the material. The committee determined that it could compromise the ability of a public standard to control such materials in terms of quality and safety.

Monograph/Section(s): Tinidazole Tablets /Organic Impurities
Expert Committee: Small Molecules 1
No. of Commenters: 1

Comment summary #1: The commenter recommended removing the reporting threshold as it will vary based on product-specific factors.
Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that the issue of the removal of reporting thresholds from monographs needs further stakeholder engagement. USP intends to conduct further stakeholder engagement.

Monograph/Section(s): Trazodone Hydrochloride Tablets/Organic Impurities
Expert Committee: Small Molecules 4
No. of Commenters: 1

Comment summary #1: The commenter recommended revising the impurity profile based on complete characterization of degradation products. Furthermore, to remove all process impurities from the impurity table.
Response: Comment not incorporated. The comment is outside the scope of the revision. The Expert Committee will consider future revisions to the monograph upon receipt of supporting data.
Comment summary #2: The commenter recommended tightening the acceptance criterion for "Any unspecified degradation product" to be consistent with the identification threshold per ICH Q3B.
Response: Comment not incorporated. The comment is outside the scope of the revision. The Expert Committee will consider future revisions to the monograph upon receipt of supporting data.
Comment summary #3: The commenter recommended removing the reporting threshold in the test for *Organic Impurities* as it will vary based on product-specific factors.
Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that the issue of the removal of reporting thresholds from monographs needs further stakeholder engagement. USP intends to conduct further stakeholder engagement.
Comment summary #4: The commenter recommended deleting the currently official *Organic Impurities* test until USP is able to include degradation impurities.
Response: Comment not incorporated. The comment is outside the scope of the revision. The Expert Committee will consider future revisions to the monograph upon receipt of supporting data.

Monograph/Section(s): Triethyl Citrate/Organic Impurities
Expert Committee: Simple Excipients

EC-initiated Change #1: Preparation of standard solutions was changed from one standard solution containing two reference standards (USP Triethyl Aconitate RS and USP Triethyl Aconitate RS) to two separate standard solutions each containing only one reference standard due to the presence of a Z-isomer of triethyl aconitate in USP Triethyl Aconitate RS that coelutes with triethyl citrate. The *System suitability* and *Analysis* sections of the test were updated to reflect the use of separate standard solutions.
EC-initiated Change #2: In Table 2, triethyl aconitate with relative retention time of 0.98 was specified as triethyl (*E*)-prop-1-ene-1,2,3-tricarboxylate.

Monograph/Section(s): Valacyclovir Hydrochloride/Water Determination, Method 1 <921>
Expert Committee: Small Molecules 1
No. of Commenters: 1

Comment Summary #1: The commenter requested revising the lower limit of “5.0%” in the acceptance criteria (5.0%-11.0%) for the water content to be consistent with the approved specification.
Response: Comment incorporated. The lower limit was revised from “5.0%” to “3.0%” with the updated range of “3.0%-11.0% consistent with additional data provided.”

Monograph/Section(s): Valganciclovir Hydrochloride/Multiple sections
Expert Committee: Small Molecules 1
No. of Commenters: 4

Comment Summary #1: The commenter commented that the run time in the *Assay* is too long and suggested to shorten the run time until the valganciclovir diastereomer peak 2 eluted completely.
Response: Comment not incorporated. The expert committee determined that the run time is consistent with the validation data and suitable for its intended use.
Comment Summary #2: The commenter noted typographical error in the test for organic impurities calculation that the Relative response factor (F_i) is in denominator in the current official monograph but in PF proposal, the F_i is in the numerator.
Response: Comment incorporated. The typo has been corrected.
Comment summary #3: The commenter recommended deleting the *Tailing factor* requirement in the test for *Organic impurities* as the Ganciclovir mono-N-methyl valinate peak appears at the tail of valganciclovir peaks and will interfere with the *Tailing factor* of valganciclovir diastereomer peak 2.
Response: Comment not incorporated. The expert committee determined that the proposed *Tailing factor* requirement is consistent with the validation data and suitable for its intended use.
Comment Summary #4: The commenter suggested adding the Ganciclovir mono-N-methylvalinate into Standard solution or *System suitability solution* and set a resolution requirement between the Ganciclovir mono-N-methyl valinate peak and valganciclovir diastereomer peak 2 in the *Limit of Ganciclovir Mono-N-methyl Valinate* test.
Response: Comment not incorporated. The expert committee determined that the method is suitable for its intended use. Adding Ganciclovir mono-N-methyl valinate to *Standard solution* or *System suitability solution* can be considered in the future revision if supporting data becomes available.
Comment Summary #5: The commenter suggested widening the acceptance criterion of resolution between valganciclovir diastereomer peak 1 and valganciclovir diastereomer peak 2 in the *Limit of Ganciclovir Mono-N-methyl Valinate* test.
response: Comment not incorporated. The comment is outside the scope of the proposed revisions. The expert committee will consider future revisions to the monograph upon receipt of the necessary supporting data.
Comment Summary #6: The commenter noted a typographical error in the calculation under the *Diastereomer Ratio* test and recommended to use the *Organic Impurities* method instead of the test for *Limit of Ganciclovir Mono-N-methyl Valinate* to be consistent with the currently official monograph.
response: Comment incorporated. The typo has been corrected.
Comment Summary #7: The commenter recommended setting the limit of ”Any individual unspecified impurity” to two decimal places to be consistent with ICH Q3A in the test for *Organic Impurities*.

response: Comment not incorporated. The comment is outside the scope of the proposed revisions. The expert committee will consider future revisions to the monograph upon receipt of the necessary supporting data.

Comment Summary #8: The commenter recommended retaining the limit of NMT 0.3% for the sum of two diastereomers of Ganciclovir mono-N-methyl valinate in the *Limit of Ganciclovir Mono-N-methyl Valinate* test, to be consistent with currently official monograph.

response: Comment incorporated. The Table 5 is updated to be consistent with the currently official monograph and a footnote " 'b' - reported as the sum of diastereomers" is added for clarity.

EC-initiated Changes #1: The calculation in the test for organic impurities is updated from

Result = $[(r_i \times F_i)/(\sum r_i \blacktriangle \sum(r_{T\blacktriangle\ (\text{USP 1-Dec-2022})} \times F_i)] \times 100$ to

Result = $[(r_i / F_i)/(\sum r_i [r_S + \blacktriangle \sum(ri_{\blacktriangle\ (\text{USP 1-Dec-2022})} / F_i)] \times 100$ to be consistent with sponsor validation data.

EC-initiated Changes #2: The calculation in the Limit of Ganciclovir Mono-N-Methyl Valinate test is updated from:

▲Result = (rU/ΣrT) × 100▲

To

▲Result = (rU/rT) × 100▲

Where ▲ rT = sum of all the peak responses from the Sample solution

to be consistent with sponsor validation data.

Monograph/Section(s): Valsartan Tablets/Reference Standards <11>
Expert Committee: Small Molecules 2

EC-initiated Change #1: The EC added another chemical name based on the reference standard label and the statement "also known as" for USP Valsartan Related Compound B RS.