ALK LIFE SCIENCE SOLUTIONS™ STERILE EMPTY VIALS: SUMMARY OF CURRENT SPECIFICATIONS AND IMPLICATIONS OF USP CHAPTER <825> UPDATE

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Introduction

The United States Pharmacopeia (USP) is an independent, scientific nonprofit organization that develops quality standards for the global production of medicines, dietary supplements, and foods. In support of these ongoing efforts, USP General Chapter <825> was developed in 2019 to guide the preparation, compounding, dispensing, and repackaging of radiopharmaceuticals. USP defines a radiopharmaceutical as “a finished dosage form that contains a radioactive substance in association with one or more ingredients and that is intended to diagnose, stage a disease, monitor treatment, or provide therapy.” This includes any nonradioactive reagent kit or radionuclide generator that is intended to be used in the preparation of any such substance.[1] Practice settings influenced by General Chapter <825> guidance include state-licensed nuclear pharmacies, federal nuclear pharmacy facilities, and a variety of relevant health care facilities such as nuclear medicine departments in hospitals and clinics, nuclear cardiology clinics, and other specialty clinics.[2]

Development and Implementation of USP General Chapter <825>

The USP convenes experts to develop and maintain quality standards. In support of these ongoing efforts, the USP Chemical Medicines Monographs 4 Expert Committee developed (Small Molecules 4) *General Chapter <825> Radiopharmaceuticals—Preparation, Compounding, Dispensing, and Repackaging—* and published the resulting document on June 1, 2019, with a planned official date of December 1, 2019.[2] In response to an appeal regarding the Chapter's content, however, this official date was postponed until resolution. After ultimately rejecting the appeal, a new official date of December 1, 2020, was set. Despite its official status, Chapter <825> is currently considered informational, as it does not meet any of the criteria needed for a General Chapter numbered below 1000 to be compendially applicable[3]:

1. The Chapter is referenced in a monograph;
2. The Chapter is referenced in another General Chapter below 1000; or
3. The Chapter is referenced in General Notices.

While Chapter <825> is classified by the USP as informational at this time, state regulatory bodies may independently determine whether guidance set forth by USP General Chapters, including that in <825>, is applicable and enforceable by the institutions they oversee.[3] Furthermore, the USP encourages early adoption of the guidance set forth by Chapter <825> to "help ensure a safe environment and protection of healthcare practitioners and others when handling radiopharmaceuticals."[4]

ALK Life Science Solutions™ Practices and USP Compliance

ALK Life Science Solutions™ manufactures sterile empty vials (SEV) composed of USP type 1 borosilicate glass in a variety of sizes, ranging from 2.0 to 100.0 cubic centimeters (cc). The manufacturing process of these vials meets requirements set by USP Chapter <660>–Containers–Glass.[5,6] All elements of the manufacturing process are driven by a robust Quality System that applies to all global functions and personnel. This Quality System is overseen and maintained by a Quality Management team that ensures that all drug products, diluents, and SEVs produced by ALK Life Science Solutions™ meet Current Good Manufacturing Practice (CGMP) requirements described by the FDA Code of Federal Regulations (CFR) Title 21 parts 210, 211, 600, and the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Q10 guidance for safety, quality, identity, potency, and purity. The management team conducts semi-annual review meetings to assess the effectiveness of current practices. Internal audits are also conducted on an annual basis, in accordance with internal auditing procedures and FDA regulations, by a certified auditor not directly responsible for the area under audit.[6] SEVs are regularly tested under USP requirements for sterility and endotoxins and are assembled in an ISO 5 (Class 100) cleanroom.[7]

ALK Life Science Solutions™ provides a Certificate of Analysis for its SEV products on request, which summarizes Quality Release Testing results.[10] This includes sterility results in accordance with USP <71> (Sterility Test)[8] and bacterial endotoxin limits according to USP <85>–Bacterial Endotoxins standards (≤0.25 EU/mL).[9,10]

Stoppers and Seals

SEVs are assembled of molded glass and are closed with a stopper and aluminum seal. The majority of the raw glass and stoppers are manufactured in the United States and are not subject to importation tariffs. The gray stoppers used to plug ALK Life Science Solutions™ SEVs are comprised of a chlorobutyl formulation, are free of natural rubber or latex, and conform to sterility and bacterial endotoxin limits set by USP <71>–Sterility Test[8] and USP <85>.[6,9,10] The seals used to seat the stoppers to the vials are composed of aluminum.[6] FluroTec®* Barrier Film is available in 10, 30, 50, and 100 cc SEVs to further minimize the risk of impurities, interactions, and medicine degradation.[7] ALK Life Science Solutions™ SEV stoppers meet closure integrity compendial requirements for type 1 closures set forth by USP <381>–Elastomeric Closures for Injections.[6,11] ALK Life Science Solutions™ maintains a reliable and consistent supply of stoppers for its SEV products. In summary, the SEVs supplied by ALK Life Science Solutions™ meet the compendially applicable requirements set by USP Chapters <660>, <71>, <85>, and <381>.

*FluroTec® is a registered trademark of West Pharmaceutical Services, Inc., in the United States and other jurisdictions. FluroTec® technology is licensed from Daikyo.

Vial Stability and Beyond-Use Date (BUD)

Beyond-use dates (BUDs) for radiopharmaceutical preparations reflect the risk of microbial contamination and are assigned with the assumption that the product should "remain chemically and physically stable, and its container-closure system should maintain its integrity for the duration of the BUD," as described by USP General Chapter <825>.[2] The BUD timing begins from the moment of the first sterile vial puncture or exposure of a critical site (eg, syringe tip, needle hub, or needle) and is dependent on the environmental conditions. The individual responsible for manipulation is responsible for assigning a BUD (based on testing data from in-house studies for sterility or peer-reviewed literature for stability). Maximum BUDs in the absence of sterility testing have been assigned by USP General Chapter <825> under a variety of preparation conditions as summarized in Table 1. BUD is influenced by preparation conditions, including level of manipulation, as well as the primary engineering control (PEC) and secondary engineering control (SEC) used. When compounding radiopharmaceutical products, the BUD for the compounded preparation must be validated, taking into account the stability of the ingredient, as well as the conditions of any intermediate containers, the final container, and storage conditions.[2]

Other Factors Affecting BUD

Assigned BUD for a radiopharmaceutical is influenced by multiple factors as identified in USP Chapter <825>, which may include but are not limited to maintenance of sterility, radiochemical purity, radionuclidic purity, age of generator eluate, number of radiolabeled particles, specific activity, container type, and cell viability.[2] Radiochemical

stability and other qualities may be affected by the container, so nuclear pharmacies using ALK Life Science Solutions™ SEVs or containers from other manufacturers should conduct independent testing to determine BUD based on all storage conditions, including container type. For radiopharmaceuticals that are conventionally manufactured and distributed to a facility or pharmacy for dispensing, the BUD cannot exceed the expiration date/time of the manufactured radiopharmaceutical product. For radiopharmaceuticals prepared from kits, the BUD of the dispensed unit dose cannot exceed the assigned BUD of the finished kit preparation.[2]

Other Container Issues Addressed in General Chapter <825>

Additional guidance in General Chapter <825> relevant to radiopharmaceutical storage relates to documentation, labeling, and repackaging of products.

Documentation

In accordance with General Chapter <825>, applicable records (hard-copy or electronic) must be maintained "for all activities involved in repackaging, preparing, preparing with minor deviations, compounding, and dispensing radiopharmaceuticals."[2] In addition, a master formulation record (MFR) is required for preparations with minor deviations or compounding. An MFR is not required for radiopharmaceuticals prepared according to manufacturer's instructions.[2]

Data that must be captured in the MFR according to Chapter <825> include the following[2]:

- Name of the radiopharmaceutical
- Name, identity, strength, purity, quality, and quantity of ingredients with validated documentation (eg, Certificate of Analysis [CoA])
- Detailed procedure (eg, heating, components, incubation time)
- Range of radioactivity
- Range of volume
- Equipment to be used
- PEC and SEC to be used, if applicable
- Quality control tests to be performed for final release (eg, radiochemical purity, pH)

- Procedures for depyrogenation and sterility procedures and validations, as applicable, including limits
- Trained personnel
- Garbing procedure, if different than standard procedure
- Container(s)
- Reference source of the BUD assignment and storage conditions

Records are also necessary for preparation with minor deviations or compounding of radiopharmaceutical products, and must include the following[2]:

- Name of the radiopharmaceutical
- Physical form (eg, capsule or solution)
- Name and quantity of ingredients, including calibration time for radioactive ingredients
- Total volume
- Reference to the MFR
- Any deviation from the MFR, if applicable
- Name of vendor or manufacturer, lot numbers, and expiration dates of all ingredients and components
- Name of the person who prepared and name of the supervising personnel (eg, authorized nuclear pharmacist or authorized user physician)
- Date and time of preparation
- Assigned internal identification number (eg, lot number)
- Unique reference (eg, prescription, order number)

- Assigned BUD and storage requirements
- Documentation of quality control (QC) results

In support of completing and maintaining these records, ALK Life Science Solutions™ provides CoA documentation for their SEVs that is available upon request at www.sterilevialsolutions.com.

Preparation With Minor Deviations

Radiopharmaceuticals are sometimes prepared with minor deviations from manufacturer instructions to accommodate clinical situations not considered in the FDA-approved labelling. As noted in General Chapter <825>, the FDA allows for these deviations under USP General Notices and Requirements, *5.20.20.1, In Compounded Preparations,* which states: “Deviation from the specified processes or methods of compounding, although not from the ingredients or proportions thereof, may occur provided that the finished preparation conforms to the relevant standards and to preparations produced by following the specified process.”[12] Aside from a few receptor-based radiopharmaceuticals where specific activity is important, General Chapter <825> acknowledges that there is “a very broad range” of acceptable values for specific activity and proportions of ingredients in radiopharmaceuticals.[2] Minor deviations may include altering the quantity of radioactivity or volume added to a vial, which may influence the choice of vial size when using SEVs during preparation.

Conclusions

The issuance of USP General Chapter <825> was undertaken with the goal of providing uniform minimum standards for the preparation, compounding, dispensing, and repackaging of sterile and nonsterile radiopharmaceuticals. While the guidance set forth by Chapter <825> is currently classified as informational and not compendially applicable, the USP encourages the adoption of these measures to ensure the safe processing of sterile and nonsterile radiopharmaceutical products for humans and animals. ALK Life Science Solutions™ maintains a reliable and consistent supply of glass vials, stoppers, and seals that conform to applicable USP Chapters describing safe manufacturing practices, including Chapters <660>, <71>, <85>, and <381>. ALK Life Science Solutions™ SEVs adhere to all applicable USP standards, including those recently detailed in USP General Chapter <825> that specifically address the preparation, compounding, dispensing, and repackaging of radiopharmaceuticals.

References

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Table 1. Maximum BUDs Assigned by USP General Chapter <825>, Based on Preparation Conditions for Radiopharmaceuticals

Preparation Conditions			
Manipulation	**PEC**	**SEC**	**BUD (hours)**
Immediate use	—	—	1
Direct infusion system, one puncture only (e.g., PET patient infusion system, Rb-82 generator)	—	—	10
Dispensing, repackaging, preparation, and preparation with minor deviations	ISO Class 5	SRPA	12
Radionuclide generator storage/elution (e.g., non-direct infusion system; Tc-99m or Ga-68)	—	SRPA with ISO Class 8 total airborne particle count	12
Radionuclide generator storage/elution (e.g., non-direct infusion system; Tc-99m or Ga-68)	—	ISO Class 8 or better buffer area with ISO Class 8 or better ante-room	24
Dispensing, repackaging, preparation, and preparation with minor deviations	ISO Class 5	ISO Class 8 or better buffer area with ISO Class 8 or better ante-room	24
Dispensing, repackaging, preparation, preparation with minor deviations, and compounding using sterile components	ISO Class 5	ISO Class 7 or better buffer area with ISO Class 8 or better ante-room	96
Dispensing, repackaging, preparation, preparation with minor deviations, and compounding using a nonsterile component and performing sterilization procedure (e.g., filtration with bubble point testing) but without performing *Sterility Tests* ⟨71⟩ testing	ISO Class 5	ISO Class 7 or better buffer area with ISO Class 8 or better ante-room	24
Radiolabeled blood components for immediate use [e.g., Tc 99m red blood cells (RBC)]	—	—	1
Radiolabeled blood components (e.g., radiolabeled leukocytes)	ISO Class 5 BSC	ISO Class 7 or better buffer area with ISO Class 8 or better ante-room	6 h after the blood sample is obtained

BUD=beyond-use date; PEC=primary engineering control; SEC=secondary engineering control.

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 Updated March 12, 2020. Accessed January 26, 2021. https://www.usp.org/chemical-medicines/general-chapter-825