



Advancing Molecular Imaging and Therapy

SNM Committee on Pharmacopeia
SNM Commission on Radiopharmaceuticals

Recommendations for Beyond-Use Dates (BUD) for Tc-99m Radiopharmaceuticals

The term Expiration Date, often called Shelf Life, is typically defined as the latest date that a manufactured drug product can be used as determined by the manufacturer. The term Beyond-Use Date is typically defined as the latest date or time that a compounded drug preparation (as described in General Chapters <795> and <797> of the United States Pharmacopeia [USP]) can be administered as assigned by the compounding pharmacist or physician. Confusion may occur, however, because many practitioners use the term Expiration Date in a broad sense when they actually mean Beyond-Use Date. For Tc-99m radiopharmaceuticals, the Beyond-Use Date is typically stated as a specific time on that same day rather than as a Date. For simplicity, the term Beyond-Use Date (BUD) will be used throughout this document with the understanding that the BUD for Tc-99m radiopharmaceuticals refers to a Time (e.g., a certain number of hours after preparation).

Background

Package inserts of commercially marketed kits for the preparation of Tc-99m radiopharmaceuticals describe instructions for the preparation and use for the radiolabeled product, including the elapsed time beyond which it should not be used. Maintenance of sterility and maintenance of radiochemical purity are the typical issues upon which these package insert use times are based. In addition, consideration of other particular factors may be appropriate for certain Tc-99m radiopharmaceuticals.

Generally, the package insert use time as stated by the manufacturer should be followed. For certain Tc-99m radiopharmaceuticals, however, transportation time, radioisotope availability, and other factors may necessitate exceeding package insert use times in order to meet patient needs. Moreover, some product package inserts do not directly state a use time, but instead recommend that the finished preparation “*should* be discarded after _ hours” [emphasis added].

Traditionally, most nuclear pharmacists and physicians have considered package insert use times for Tc-99m radiopharmaceuticals to be recommendations rather than requirements (e.g., use of the word “should” as described above), and have thus assigned a BUD as deemed appropriate. For situations when the BUD of a Tc-99m radiopharmaceutical has exceeded the package insert use time, the BUD has generally been validated (with various levels of rigor) by in-house testing or reliance on information published in the literature.

There exists little guidance regarding for assigning a BUD that exceeds the package insert use time. However, the following provide some foundation for discussion of concerns and developing a recommendation.

The Society of Nuclear Medicine Procedure Guideline for the Use of Radiopharmaceuticals 4.0 (2-7-2008) states:

Radiopharmaceuticals should not be used beyond the expiration date or time recommended by the manufacturer **unless quality control testing demonstrates that the product still meets the specifications of the United States Pharmacopeial Convention (USP) at the time of use.** [emphasis added]

The American Pharmaceutical Association, Section on Nuclear Pharmacy Practice's Nuclear Pharmacy Compounding Guidelines (9-23-2001) state:

The beyond-use time/date limit of any compounded reagent kit or radiopharmaceutical may be extended when there is valid supporting scientific stability information that is directly applicable to the specific preparation (i.e., the same drug concentration range, pH, excipients, vehicle, water content, etc.).

All stability data should be carefully interpreted in relation to the actual compounded formulation. The beyond-use times and dates should be assigned conservatively.

USP <797> does not directly address this issue, but certain statements regarding Beyond Use Dates (BUDs) may have some applicability:

BUDs for CSPs [Compounded Sterile Products] that are prepared strictly in accordance with manufacturers' product labeling shall be those specified in that product labeling **or from appropriate literature sources or direct testing.** [emphasis added]

When CSPs deviate from conditions in the approved labeling of manufactured products contained in CSPs, compounding personnel may consult the manufacturer of particular products for advice on assigning BUDs based on chemical and physical stability parameters.

When assigning a beyond-use date, compounding personnel should consult and apply drug-specific and general stability documentation and literature, where available. They should also consider the nature of the drug, its degradation mechanism, the container in which it is packaged, the expected storage conditions, and the duration of therapy.

It should be recognized that the truly valid evidence of stability for predicting beyond-use dating can be obtained only through product-specific experimental studies.

Semiquantitative procedures such as thin-layer chromatography (TLC) may be acceptable for many CSPs.

To ensure consistent practices in determining and assigning BUDs, the compounding facility should have written policies and procedures governing the determination of the BUDs for all compounded products.

Concerns

1. Sterility

One concern with assigning a BUD that exceeds the package insert use time is the increased risk of microbial growth. For Tc-99m radiopharmaceuticals, however, this

should not be a substantial issue if USP <797> is followed. Specifically, USP <797> allows a BUD of up to 12 hours for radiopharmaceuticals that are classified as low-risk level Compounded Sterile Preparations (CSPs) when prepared in a segregated compounding area. A BUD up to 48 hours at room temperature is allowed for radiopharmaceuticals that are classified as low-risk level CSPs when prepared in a clean room as described in USP <797>.

2. Radiochemical purity

Maintenance of radiochemical purity is typically the primary concern for Tc-99m radiopharmaceuticals. Radiochemical stability is affected by a variety of factors including storage temperature, amount of radioactivity, radioactive concentration, presence or absence of anti-oxidants or other stabilizing agents, container type, etc. Hence, assigning a BUD that exceeds the package insert use time must be based on radiochemical stability studies in which these variables are controlled and are representative of the conditions of actual use. For factors that allow a range of values (e.g., storage temperature, amount of radioactivity, radioactive concentration), studies should be conducted at the extremes of the ranges.

3. Radionuclidic purity

Because the ratio of Mo-99 to Tc-99m continuously increases with time, the Nuclear Regulatory (NRC) and USP require that Mo-99 content not exceed 0.15 μCi per mCi Tc-99m at the time of administration. Hence, assignment of a BUD that exceeds the package insert use time must take into account Mo-99 content and ensure compliance with this radionuclidic purity requirement throughout the BUD.

4. Age of Tc-99m pertechnetate

As a solution of Tc-99m pertechnetate ages, Tc-99m atoms decay to become Tc-99 atoms. More importantly, there will also be increasing amounts of peroxides formed as radiation interacts with water molecules. Tc-99 and peroxides present in a given radioactivity amount of aged Tc-99m can interfere with the radiolabeling of many reagent kits. Hence, the assignment of a BUD that exceeds the package insert use time for Tc-99m pertechnetate intended for radiolabeling reagent kits must take into account the build-up of Tc-99 and peroxides over time for a given radioactivity amount of Tc-99m.

5. Number of MAA particles

Manufacturers of MAA reagent kits state that 200,000 – 700,000 particles should be administered to an adult. The assignment of a BUD for Tc-99m MAA preparations must take into account the increasing ratio over time of the number of particles per radioactivity patient dose. For example, if a reagent kit of MAA is prepared such that a radioactivity patient dose = 200,000 particles at the time of calibration, that same radioactivity patient dose would contain 700,000 particles at 10.85 hours after calibration.

6. Tc-99m DTPA for measurement of GFR

Tc-99m DTPA appears to undergo changes in plasma protein binding with respect to storage time, even though radiochemical purity testing results remain acceptable. Therefore, some DTPA product package inserts recommend that Tc-99m DTPA should

be injected within 1 hour of preparation when used for measurement of glomerular filtration rate (GFR).

Society of Nuclear Medicine Committee on Pharmacopeia (SNM COP) Recommendation

SNM COP recommends that package insert use times as stated by the manufacturer should be followed for Tc-99m radiopharmaceuticals. However, transportation time, radioisotope availability, and other factors may necessitate exceeding package insert use times in order to meet patient needs. Therefore, SNM COP supports pharmacist and physicians in assigning BUDs that exceed package insert use times for Tc-99m radiopharmaceuticals if all of the following criteria, as applicable, are met:

1. The assigned BUD does not exceed the BUD for the risk-level CSP as described in USP <797>.
2. The assigned BUD is supported by results of radiochemical stability studies showing maintenance of acceptable radiochemical purity over time when using the same conditions (e.g., storage temperature, amount of radioactivity, radioactivity concentration, presence or absence of anti-oxidants or other stabilizing agents, container type, etc.) as actually used for the radiopharmaceutical to be administered. For factors that allow a range of values (e.g., storage temperature, amount of radioactivity, radioactivity concentration), studies should be conducted at the extremes of the range.
3. The assigned BUD does not exceed the USP/NRC limit for Mo-99 content at the time of administration.
4. The assigned BUD for Tc-99m pertechnetate intended for radiolabeling reagent kits is supported by results of radiolabeling studies using the same age-related factors (e.g., with respect to Tc-99 and peroxide content).
5. The assigned BUD for Tc-99m MAA does not exceed the time at which a patient dose would exceed the maximum recommended number of MAA particles.
6. The assigned BUD for Tc-99m DTPA to be used in the measurement of GFR is supported by results of stability studies involving plasma protein binding.
7. The facility should have policies and procedures appropriate for the assignment of BUDs and keep applicable documentation of validation study results and calculations.
8. Studies of radiolabeling efficiency and radiochemical stability should employ quality control methods described in the package insert, or USP testing methods (or equivalent), and be sufficiently rigorous to allow statistical confidence in the results.
9. The facility should have a mechanism to collect and evaluate complaints associated with the use of radiopharmaceuticals having assigned BUDs that exceed package insert use times. Policies and procedures should also be in place to re-evaluate the assigned BUD based on complaints, which may include repeating and/or performing additional studies of radiolabeling efficacy and/or radiochemical stability.