Guidelines for the Use of Preservative-Free Pharmaceuticals and Parenteral Fluids in Laboratory Animals

This guideline is intended to reiterate the NIH "best practices" used to ensure the sterility and integrity of preservative-free pharmaceuticals and parenteral fluids administered to laboratory animals. Consideration of limited storage times after opening a preservative-free pharmaceutical or parenteral fluid is warranted, due to the variety of conditions under which these products are stored and the potential for use of inappropriate aseptic technique[1-5]. The US Pharmacopeia—National Formulary (USP- NF) states that preservative-free saline for injection or IV fluids in opened containers should be used within twelve (12) hours in an ISO Class 5 environment [5-9]. Whereas, other sources indicate that the shelf life of opened containers may range up to eight weeks.[5,9] While the use of parenteral fluids past the 12- hour standard recommended by the USP can be viewed as low risk, the consequences of contaminated fluid administration can be animal morbidity or mortality[2-5] as well as altered research data. Some recent case studies have revealed that up to 5.5% of in-use multidose vials may be contaminated.[10] The "best practices" listed below have been used at the NIH to safeguard the stability and efficacy of preservative- free products used in laboratory animals:

Definitions:

1. *Preservative-free pharmaceuticals*: medications that are formulated without the addition of preservatives
2. *Preservative*: a substance added to inhibit microbial growth
3. *Parenteral fluids*: administered through a route other than the gastrointestinal tract, usually by injection or infusion[11]
4. *Sterility:* the absence of viable microorganisms[8]
5. *Beyond-Use Date (BUD):* the date after which a compounded products should not be used[8]

Best Practices:

General Handling

- Procurement of smaller volume containers of preservative-free pharmaceuticals or parenteral fluids that can be handled as a single-use container or discarded at the end of the workday is recommended.
- Any preservative-free and parenteral fluid container that has been opened or accessed (e.g., needle-punctured), and which is not immediately discarded, should be labeled with the date opened.
    - Based on current literature review and NIH IRP practices/performance standards, a maximum BUD of not more than 28 days is suggested unless otherwise specified by an IC ACUC.[12,13]
    - The new USP- NF (797) for sterile compounding guidelines suggest different BUD based on risk levels (low, medium or high risk) and storage (room temperature, refrigeration or freezing).[8] IC ACUCs may consider these factors, in addition to existing literature and practices, in determining appropriate BUDs for preservative-free and parenteral fluids.
- Only sterile needles, syringes, pipettes, and pipette tips shall be used to withdraw fluids from a container for parenteral administration.[1,13,14]
- Special attention must be paid to avoid contaminating the pharmaceutical or fluid container while penetrating the stopper or access diaphragm. The user should perform proper hand

hygiene: by washing hands with soap and water, using hand sanitizers, and/or donning clean gloves and sanitizing them frequently with isopropyl alcohol along with all surfaces/diaphragms/stoppers is associated with a much lower risk of contamination. Similarly, these drugs should be prepared/mixed in the cleanest area possible, ideally within a biosafety cabinet to minimize the risk of contamination and maximize the BUD that could be applied.[15,16] The stopper or access diaphragm of a fluid container must be cleaned with 70% alcohol[1,5] and allowed to dry prior to each use, using care to avoid contaminating the cleaned area before penetrating the stopper.[1,2,5]

- At no time shall a fluid container be reentered with a needle that has been previously used to inject an animal or accessed with any item with known or suspected to be unsterile.
- Using one sterile needle to quickly fill multiple sterile syringes, without removing the needle from the container, can help protect the integrity of the stopper or access diaphragm. Care must be used when changing the syringe not to contaminate the needle hub or syringe tip[2]. A needle which is not attached to a sterile syringe should not be left in the stopper or access diaphragm of a fluid container. Studies have shown that contact of ungloved fingers or other objects with the needle hub or the tip of the syringe or the uncapped needle result in high risk of contamination of the sterile medication within.[17]
- The introduction of air into a container to facilitate withdrawal of the fluids should be kept to a minimum.[2]

Storage and Disposal

- Preservative-free pharmaceutical or fluid containers should be stored in accordance with the manufacturer's recommendations. Storage location should also take into consideration the potential for environmental contamination; consider storing in a closed container, sealed baggie or cabinet.[5,12,13]
- When provided, manufacturer instructions as to handling and discarding of reconstituted preservative-free pharmaceuticals should be followed to ensure the stability, and efficacy of the product.
- A preservative-free pharmaceutical or parenteral fluid container that has not been opened or accessed (e.g., needle-punctured), should be discarded in accordance with the manufacturer's expiration date.
- Preservative-free pharmaceutical or parenteral fluid containers containing dextrose, hetastarch, or heparin should be discarded by the end of the day the container was opened or accessed (e.g., needle-punctured).[2,6,14,18]

Physical Assessment of Materials

- Containers and their contents should be examined prior to use for evidence of physical damage, contamination, abnormal particulate(s), discoloration, or abnormal turbidity[9].
- Pharmaceutical or fluid containers found to have any of the following characteristics should never be used:
    - Unlabeled or mislabeled
    - Noticeable coring, damage or deterioration of the stopper or access diaphragm
    - Outdated
    - Improperly stored
- Pharmaceutical or parenteral fluid containers must be discarded whenever sterility is

compromised or questionable.

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