National Association of Nuclear Pharmacies

Position Paper on
Aseptic Processing of Radiopharmaceuticals in a Nuclear Pharmacy

Introduction

The National Association of Nuclear Pharmacies (NANP) has developed the following position paper on the topic of aseptic processing of radiopharmaceuticals in.order to assist practitioners and boards of pharmacy in understanding the degree of care that should be taken while compounding radioactive drugs. To date, the topic of aseptic processing of radiopharmaceuticals has not been addressed in the pharmacy literature to the extent that it has been for nonradioactive medications. Literature from several well-recognized pharmacy organizations was considered during the development of this position paper, and the opinions and positions of these organizations will be referred to throughout this document.

Discussion of General Guidelines

The position of the National Association of Boards of Pharmacy (NABP) is that prescription compounding is a pharmacist's responsibility and should be regulated by state boards. To distinguish between compounding and manufacturing, NABP defined these terms in its Model State Pharmacy Practice Act:

> *"Compounding - the preparation, mixing, assembling, packaging, or labeling of a drug (including radiopharmacetaicals) or device (i) as the residt of a practionier/patient/pharmacist relationship in the course of professional practice, or (ii) for the purpose of, or as an incident to, research, teaching, or chemical analysis and not for sale or dispensing. Compounding also includes the preparation of drugs or devices in anticipation of prescription drug orders based on routine, regularly observed prescribing patterns.*
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> *Manufacturing - the production, preparation, propagation, conversion, or processing of a drug or device either directly or indirectly, by extraction from substances of natural origin or independently by means of chemical or biological synthesis, and includes any packaging or repackaging of the substance(s) or labeling or relabeling of its container, and the promotion and marketing of such drugs and devices. Manufacturing also includes the preparation and promotion of commercially available products from bulk compounds for resale by pharmacies, practitioners or other persons."*

NABP has published two model regulations or guidelines about the preparation of sterile products. One is Good Compounding Practices Applicable to State Licensed Pharmacies, a general compounding document for state boards of pharmacy that was prepared at the request of the FDA. The other is Model Rules for Sterile Pharmaceuticals. Both guidelines apply to

pharmacy practice regardless of the setting. However, NABP model regulations do not have the force of law. They merely serve as a basis for individual state boards to develop rules and regulations.

In summary, NABP guidelines have eight key points:

- A policy and procedure manual should be established for compounding, dispensing, and delivery of sterile pharmaceutical prescription orders.
- Pharmacists and supportive personnel should be trained and have sufficient reference materials about sterile products.
- Drugs and supplies should be stored, labeled, and disposed of properly.
- Sterile compounding should be done in an area separate from other activities. (However, a "cleanroom" environment is not specified.)
- Personnel should adhere to hygienic and aseptic techniques.
- Documentation should specify when and why manufacturer-labeled expiration dates are exceeded.
- Pharmacists should check finished products.
- Records of compounding should be carefully maintained as part of a documented, ongoing quality-assurance program.

The American Society of Hospital Pharmacists, ASHP, which publishes guidelines for pharmaceutical compounding in institutional settings has studied and is considered the authority on the subject of sterile prep and aseptic technique. The ASHP invited key persons to participate in a conference; its purpose was to list apparent problems with pharmacy-prepared sterile products and to identify possible solutions. Attendees included representatives from the FDA, United States Pharmacopoeia Convention (USP), American Hospital Association (AHA), NABP, Intravenous Nurses Society, Association for Practitioners of Infection Control, American College of Apothecaries, Joint Commission on the Accreditation of Healthcare Organizations (JCAHO), AACP, Parenteral Drug Association, Pharmaceutical Manufacturers Association, American Biological Safety Association, Canadian Society of Hospital Pharmacists, American Nurses Association, and some members and staff of ASHP.

Conference participants listed 12 problems with the pharmacy sterile compounding practices. These problems may be categorized into four groups:

- A lack of appropriate policies and procedures.
- A lack of personnel training and education materials.
- A lack of consistent regulatory definitions, standards, and enforcement by professional and governing groups.
- A lack of commercially available sterile products.,

As a result of this conference the ASHP published a *Technical Assistance Bulletin on Quality*

Assurance for Pharmacy-Prepared Sterile Products which designates three levels of risk to patients, increasing from the least (Risk Level 1) to the greatest (Risk Level 3) potential for harm.

This categorization by risk levels allows pharmacists to match sterile compounding procedures to the products they prepare. When compounding a product under conditions that do not meet risk level requirements, pharmacists are required to use their best judgment of risk to benefit for the patient.

The USP also provided input on the subject. The USP decided that preparation of sterile intravenous products for home use involved special concerns (e.g., extended product storage and patient manipulations prior to use), Therefore, USP established a Home Health Care Advisory Panel in 1989 to draft a monograph or guideline on compounding sterile products for home use. The first draft of this monograph was published in March 1992. Following the review of 22 written comments, the Panel published a second draft for public comment in May 1993. The final draft was published in November 1993, and it now appears in the 1995 United States Pharmacopeia/National Formulary .

Because so many different groups have contributed to the subject, determining the applicable guideline can be difficult. The NABP references two guidelines, one is Good Compounding Practices Applicable to State Licensed Pharmacies. The other is Model Rules for Sterile Pharmaceuticals. The Good Compounding Practices Applicable to State Licensed Pharmacies is the only document referencing radiopharmaceuticals. Specifically, "If radiopharmaceuticals are being compounded, conditions set forth in the *NABP Model Rules for NuclearlRadiologic Pharmacy* must be followed."

The *NABP Model Rules for Nuclear, Radiologic Pharmacy* references the NABP Rules for Sterile Pharmaceuticals. The *Rules for Sterile Pharmaceuticals* does not establish specific risk categories by product type. The model does establish the standards for hoods and their environment. The model does not differentiate by risk factor. The only document that establishes specific procedures by product risk is the ASHP *Technical Assistance Bulletin on Quality Assurance for Pharmacy Prepared Sterile Products.*

Further confirmation for using the ASHP guidelines can be found in a chapter written by Clyde Buchanan entitled "Sterile Compounding Facilities" in the book *Principles of Sterile Preparation.* The chapter answers the question, "What guidelines apply to specific patient populations?"

> *"For hospital inpatients, ASHP guidelines should be followed For retail pharmacy patients (where products contain suilahle preservatives), NABP guidelines are appropriate. For home health care patients, USP guidelines require cleanrooms at all levels." (page* 26)

Highlights from the *ASHP Technical Assistance Bulletin on Quality Assurance for Pharmacy Prepared Sterile Products* are contained below.

The ASHP *Technical Assistance Bulletin on Quality Assurance for Pharmacy-Prepared Sterile Products* does not apply to the manufacture of sterile pharmaceuticals, as defined in state and federal laws and regulations, nor does it apply to the preparation of medications by

pharmacists, nurses, or physicians in emergency situations for immediate administration to patients. Not all recommendations may be applicable to the preparation of radiopharmaceuticals.

ASHP recommendations are referenced with supporting scientific data when such data exist. In the absence of published supporting data, recommendations are based on expert opinion or generally accepted pharmacy procedures. Pharmacists are urged to use professional judgment in interpreting these recommendations and applying them in practice. It is recognized that, in certain emergency situations, a pharmacist may be requested to compound products under conditions that do not meet the recommendations. In such situations, it is incumbent upon the pharmacist to employ professional judgment in weighing the potential patient risks and benefits associated with the compounding procedure in question.

Risk Level 1

Risk level 1 applies to compounded sterile products that exhibit characteristics 1, 2, and 3 stated below. All level 1 products should be prepared with sterile equipment (e.g. syringes, vials), sterile ingredients and solutions, and sterile contact surfaces for the final product. Of the three risk levels, risk level 1 necessitates the least amount of quality assurance. Risk level 1 includes the following:

1. Products
   - A. Stored at room temperature and completely administered within 28 hours from preparation; or
   - B. Stored under refrigeration for 7 days or less before complete administration to a patient over a period not to exceed 24 hours; or
   - C. Frozen for 30 days or less before complete administration to a patient over a period not to exceed 24 hours.
2. Unpreserved sterile products prepared for administration to one patient, or batch prepared product containing suitable preservatives prepared for administration to more than one patient.
3. Products prepared by closed system aseptic transfer of sterile, nonpyrogenic, finished pharmaceuticals obtained from licensed manufacturers into sterile final containers (e.g. syringe, minibag, portable infusion device) obtained from a licensed manufacturer.

Risk Level 2

Risk level 2 sterile products exhibit characteristic 1, 2, or 3 stated below. All risk level 2 should be prepared with sterile equipment, sterile ingredients, and solutions, sterile contact surfaces for the final product and by using closed-system transfer methods. Risk level 2 include the following:

1. Products stored beyond 7 days under refrigeration, or stored beyond 30 days frozen, or administered beyond 28 hours after preparation.
2. Batch prepared products without preservatives that are intended -for use by more than one patient.
3. Products compounded by combining multiple sterile ingredients, obtained from a licensed manufacturer, in a sterile reservoir, obtained from a licensed manufacturer, by using a closed system aseptic transfer before subdivision into multiple units to be dispensed to patients.

Risk Level 3

Risk level 3 products exhibit characteristics 1 or 2.

1. Products compounded from nonsterile ingredients or compounded with nonsterile components, containers, or equipment.
2. Products prepared by combining multiple ingredients - sterile or nonsterile -by using an open system transfer or open reservoir before terminal sterilization or subdivision into multiple units to be dispensed.

Radiopharmaceuticals have unique properties. Specifically, they are administered not only in less than 28 hours but usually in less than 8 hours, administered in very small volumes, and are compounded under very simple closed system transfers. Therefore, these conditions coupled with the conditions listed in Risk level 1 clearly place radiopharmaceutical as risk level 1 products.

ASHP goes on to define eleven categories of procedures and processes needed for proper aseptic technique when compounding risk level (RL) 1 products.

RL 1.1 Policies and Procedures

Up to date policies and procedures for compounding sterile products should be written and available to all personnel involved in compounding activities. The policies and procedures should address the ten remaining categories.

RL 1.2 Personnel Education, Training, and Evaluation

Pharmacy personnel preparing or dispensing sterile products should receive suitable didactic and experiential training and competency evaluation through demonstration, testing, (written or practical), or both.

RL 1.3 Storage and Handling

Solutions, drugs, supplies, and equipment used to prepare or administer sterile products should be stored in accordance with manufacturer or USP requirements. Unnecessary personnel traffic in the controlled area should be minimized. Particle generating activities should not be performed in the controlled area.

RL 1.4 Facilities and Equipment

The controlled area should be a limited access area sufficiently separate from other pharmacy operations to minimize the potential for contamination from unnecessary flow, of materials

and personnel. Additionally, sterileproducts should be prepared in a Class 100 environment. Such an environment exists inside a certified horizontal or vertical-laminar-airflow hood.

RL 1.5 Garb

Procedures should generally require that personnel wear clean clothing covers that generate low amounts of particulates in the controlled area.

RL 1.6 Aseptic Technique and Product Preparation

Only materials essential for preparing the sterile product should be placed in the laminar airflow hood. All aseptic procedures should be performed at least 6 inches inside the front edge of the laminar airflow.

RL 1.7 Process Validation

For most aseptic preparation procedures, process validation is actually a method of assessing the adequacy of a person aseptic technique. Process simulation testing is valuable for assessing the compounding process, especially aseptic fill operations. It allows for the evaluation of opportunities for microbial contamination during all steps of sterile product preparation. Process simulation testing is carried out in the same manner as normal production except that an appropriate microbial growth medium is used in place of the actual products used during sterile preparation. The medium samples are then incubated and evaluated. If no microbial growth is detected, this is evidence that adequate aseptic technique was used.

RL 1.8 Expiration Dating

All pharmacy prepared sterile products should bear an appropriate expiration date. The expiration date assigned should be based on currently available drug stability information and sterility considerations.

RL 1.9 Labeling

Sterile products should be labeled.

RL 1.10 End Product Evaluation

The final product should be inspected and evaluated for prior to dispensing.

RL 1.11 Documentation

Documentation should be maintained according to state regulatory requirements.

Discussion of Process Validation

End-product sterility testing of parenteral products is often not practical, process validation has become a popular quality-control technique. This technique systematically demonstrates that a process will reproducibly meet its claim.

Process validation - often referred to as media fills - involves manipulation of microbial growth media according to the aseptic process being validated.

- Scheduling of Process Validation

  Process validation should be scheduled under a "worst case" scenario -under conditions posing the greatest chance for product failure. Therefore, these tests are conducted independent of production runs, when the testing line is set up specifically for them.

  In the pharmacy, such process validation testing should take place immediately after a day's production is completed. According to the United States Pharmacopoeia Convention (USP), process being validated using media fills should be scheduled at times representative of peak fatigue, stress, and pacing demands.

- Sampling Techniques

  Process validation of aseptic technique and aseptic processes is based on the concept that, when contaminated, a growth medium will support the organisms introduced by the operator. Furthermore, the media must be manipulated according to the aseptic technique or process being validated. The media should be packaged and handled just like the ingredients of the actual sterile products. These tests can be done with commercially available kits or actual pharmacy supplies.

- Commercial Kits

  Several commercially available kits facilitate process validation using different sampling techniques. The Compounded Validation Test Media Kit (Baxter Healthcare) includes supplies for simulating the preparation of both simple and complex IV admixtures. The Attack Aseptic Technique Testing and Challenge Kit (Marsam Pharmaceutical) includes materials needed to simulate sterile product preparation using ampules, vials, and powder fill vials.

Discussion of Equipment Used for Aseptic Processing

Laminar Air Flow Hoods

A laminar-airflow hood - with either horizontal or vertical airflow - is a cost-effective, efficient way to provide the Class 100 environment required for pharmacy use. Horizontal laminar flow hoods blow air toward the user. Whereas, vertical flow hoods do not. Therefore, vertical flow hoods are the

hood of choice for nuclear pharmacy practice. Laminar flow hoods are part of a large family of equipment call biohazard cabinets. Biohazard or laminar hoods, interchangeable for this discussion, are grouped into three major classes.

Class 1 - HEPA filter on output air but not input air. They protect the user and environment but not the product. Class 1 hoods have no application during aseptic preps.

Class 2 - HEPA filter on both the in and out air. Class 2 hoods protect the user, product and environment. Class 2 hoods are suitable for aseptic preparations. Class 2 hoods are further divided into type A or type B. Type A hoods recirculate work air and exhaust to the room. Type B may or may not recirculate and exhausts to and area outside the controlled area.

Class 3 - Totally enclosed, vented, and gas tight. Operations are conducted through attached rubber gloves and the cabinet is maintained under negative pressure. These cabinets have limited use in the preparation on aseptic products.

Regardless of the hood type used the following general principles should be followed to provide the proper working environment:

1. All aseptic manipulations should be performed at least 6 inches within the hood. This distance prevents reflected contamination from the worker's body and "backwash" contamination from turbulent air patterns developing at the laminar-airflow hood-room interface.

2. A laminar-airflow hood should operate continuously. If the hood is turned off, it should not be used for a specified time when reactivated, depending on the manufacturer's recommendations (e.g., 30 min). This downtime allows all room air to be purged from the critical area.

3. Before use, all interior working surfaces of the hood should be cleaned with 70% isopropyl alcohol or another disinfecting agent and a clean, lint-free (nonshedding) cloth. Cleaning should be performed from back to front, so that contaminants are moved away from the HEPA filter, Throughout the compounding period, the hood should be cleaned often. Some materials are not soluble in alcohol and may initially require water for removal. To avoid damage, Plexiglas sides should be cleaned with warm, soapy water rather than alcohol.

4. Nothing should touch the HEPA filter, including cleaning solution, aspirate from syringes, and glass from ampules. Ampules should not be broken directly toward the filter.

5. A laminar-airflow hood should be positioned away from excess traffic, doors, air vents, fans, and air currents capable of introducing contaminants.

6. Hand and wrist jewelry should not be worn, jewelry may introduce bacteria or particles.

7. Actions such as talking and coughing should be directed away from the critical area, and any unnecessary motion should be avoided to minimize airflow turbulence.

8. Only objects that are essential to product preparation should be placed in the hood - no paper, peris, labels, and trays.

9. Laminar-airflow hoods should be tested and certified by qualified personnel every 6 months, whenever the hood is moved, and if filter damage is suspected. Tests can certify airflow velocity and HEPA filter integrity.

10. Food and drink should not be permitted within the aseptic preparation area.

Conclusion

Radiopharmaceuticals are unique products that most closely fit the ASHP definitions for Risk Level,1 products. This Classification is reasonable and logical because radiopharmaceulticals are injected in usually less than 8 hours from the time of preparation, have relaltively small volumes (0.1 to 3.0 cc), and the reagent kits are very simply compounded. Risk level 1 products do not require clean rooms, environmental monitoring; or bunny suits Risk level I products do require a class 100 environment and a compounding area restricted from excessive traffic. Additionally, particulate-producing materials, inside the compounding area should be minimized.

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Approved by the NANP Board of Directors on