REPORT OF THE CANADIAN ASSOCIATION OF RADIOPHARMACEUTICAL SCIENTISTS (CARS) TASK FORCE ON USP<797> IMPLICATIONS FOR RADIOPHARMACEUTICALS IN CANADA

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EXECUTIVE SUMMARY

USP<797> is an U.S. standard that applies specifically to compounding of sterile pharmaceuticals (CSPs), including radiopharmaceuticals. 99mTc-labelled radiopharmaceuticals generally fall under the ‘low-risk compounding’ category provided they are prepared by qualified personnel in a Grade A environment within a biosafety cabinet or compounding aseptic isolator (CAI) that is located in a Grade D buffer area, or a segregated compounding area. Generator systems for 99mTc must be eluted within a Grade D environment. Cell labeling falls in a higher risk category and requires that the biocabinet be housed within a Class C environment. All classified environments require HEPA-filtered air in the clean room and buffer area. USP<797> also covers requirements for monitoring microbial and non-viable particulates, personnel training and evaluation in aseptic technique, and equipment and product quality control.

At this time, the majority of nuclear medicine facilities and radiopharmacies in Canada are not compliant with USP<797>. This is also the case in the U.S. and in Europe where a great range in regulatory oversight and compliance exists. The preparation of radiopharmaceuticals has traditionally fallen under the practice of pharmacy, however the provincial colleges of pharmacy have not included the preparation of radiopharmaceuticals as part their regulatory oversight, and Health Canada has yet to step into this role. Regardless, Nuclear Medicine departments and radiopharmacies in Canada have consistently demonstrated an excellent safety record with respect to product preparation and quality control.

The most serious blockade toward implementation of USP<797> in Canadian nuclear medicine departments is the cost to renovate existing infrastructure. Estimated costs to healthcare nationally could easily exceed $12M and do not include costs associated with the purchase of capital equipment such as biological safety cabinets for the preparation and dispensing of radiopharmaceuticals. Significant changes in ductwork and air supply may not be feasible in many institutes and are limited by 5-10 year timelines and associated budgets for provincially approved building changes. Additional costs include implementation of environmental monitoring, personnel training, and quality assurance monitoring. Adoption of USP<797> in its entirety would result in a significant increase in the cost of delivery of nuclear medicine services ultimately increasing provincial healthcare costs, reducing access, and increasing wait times for procedures. Regardless, compliance with USP<797> is considered best practice for preparation of compounded sterile products in Canada, and implementation of certain elements of USP<797> should be considered by all institutions to improve their safety profile if it can be implemented in a cost-effective manner.
APPOINTMENT AND CARS MANDATE TO TASK FORCE

The CARS Task Force was established in 2012 with the mandate to
1) determine and report on the readiness status for compliance by nuclear medicine
   facilities and radiopharmacies in Canada to USP<797>;
2) determine potential financial, equipment, personnel, operational, and other resource
   implications for full compliance to USP<797> by the above facilities in Canada;
3) advise on adjustments/accommodations by the U.S. and other jurisdictions to address
   real-life application of USP<797>; and
4) recommend to CARS an effective strategy that ensures that implementation of
   USP<797> will be cost-effective and promote high standards of patient care

Members of Task Force

Ingrid Koslowsky (Chair)
James Mang’era (Secretary – Non-CARS)
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BACKGROUND

The practice of Nuclear Medicine has been a valuable tool in the diagnosis and treatment in patients since the development of the rectilinear scanner and Anger camera in the mid 50’s. To date, there are approximately 209 centres in Canada that hold a licence to perform diagnostic nuclear medicine procedures (http://www.nuclearsafety.gc.ca). Of these, approximately 60% are supplied with radiopharmaceuticals from centralized radiopharmacies¹. The remaining NM departments purchase $^{99}$Mo/$^{99m}$Tc generators weekly to prepare agents labeled with $^{99m}$Tc-labeled agents, as well as commercially available radionuclides. Most products do not contain antibacterial preservatives; they are prepared daily using aseptic technique, and designated as multi-dose vials from which multiple doses are drawn throughout the day.

Many $^{99m}$Tc-labeled products have been in use for 50 years with few to no adverse reactions reported. Thus these products exhibit a high safety profile with respect to product preparation and use. Most Nuclear Medicine departments have protocols that utilize strict aseptic technique to prepare a sterile, injectable product using licenced sterile, and pyrogen-free radionuclides and radiopharmaceutical kits: these departments do not typically have Class A environments in the their Hot Lab area. Products are prepared in public or private nuclear medicine clinics by technologists trained in the handling and preparation of radiopharmaceuticals and certified by the Canadian Association of Medical Radiation Technologists (CAMRT) as competent in their field. Most sites follow the manufacturer’s instructions in the package insert for the reconstitution of kits. The remaining centres are served through centralized radiopharmacies operating under aseptic handling procedures. These institutions are supervised by qualified radiopharmacists trained in Good Manufacturing Practices, must comply with the federal Food and Drug Regulations; most have a Drug Establishment Licence and undergo site inspections performed by Health Canada.

The preparation of radiopharmaceuticals has been considered a compounding activity, which falls under the practice of pharmacy. Oversight of pharmacy operations is a provincial responsibility but, to-date, professional pharmacy associations in Canada have not included the preparation of radiopharmaceuticals as part their oversight. This may be due to their limited expertise in radiation safety and radiopharmaceutical quality assurance. These activities fall under the ‘practice of medicine’, with the Nuclear Medicine Physician ultimately responsible for the quality of the radiopharmaceutical.

USP<797> is a U.S. standard which applies specifically to compounding of sterile pharmaceuticals (CSPs), including radiopharmaceuticals, and is intended to apply to all places where CSPs are prepared, including hospitals and other healthcare institutions, patient treatment clinics, pharmacies and radiopharmacies, physicians’

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¹ Personal communication
practice facilities, etc. The goal is to provide product safety and quality standards for preparing CSPs.

USP<797> provides the basis for the development and implementation of procedures for the safe preparation of low-risk, medium-risk, and high-risk level CSPs and immediate-use CSPs, which are classified according to the potential for microbial, chemical, and physical contamination. The standards cover

- Responsibility of Compounding Personnel
- Microbial Contamination Risk Levels
- Personnel Training and Evaluation in Aseptic Manipulation Skills
- Risk levels of CSPs including Radiopharmaceuticals
- Environmental Quality and Control of facilities
- Equipment and product Quality Control
- Storage and Beyond-Use Dating
- Sterility and Stability of Dispensed and Distributed CSP
SCOPE OF USP<797> ON COMPOUNDING OF STERILE PREPARATIONS (CSPS)

Compounding Risk Levels in Radiopharmacy

Sterile compounding requires achievement of sterility when working with non-sterile components, and maintenance of sterility when compounding with sterile components. The standards apply not only to the microbial risk associated with sterile compounding but also the risk of contamination with non-viable particulates, as medium to large sized particulates can harbor bacteria. Table 1 provides the standards for various classifications of rooms regarding particulate matter.

Table 1: Basic Environmental Standards for the Manufacture of Sterile Products

<table>
<thead>
<tr>
<th>Grade</th>
<th>at rest (Note 5)</th>
<th>in operation</th>
<th>at rest (Note 5)</th>
<th>in operation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Maximum permitted number of particles / m³ equal to or above (Note 3)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>0.5 µm</td>
<td>5 µm</td>
<td>0.5 µm</td>
<td>5 µm</td>
</tr>
<tr>
<td>A (Note 1)</td>
<td>3 520</td>
<td>20</td>
<td>3 520</td>
<td>20</td>
</tr>
<tr>
<td>B (Note 2)</td>
<td>3 520</td>
<td>29</td>
<td>352 000</td>
<td>2 900</td>
</tr>
<tr>
<td>C (Note 2)</td>
<td>352 000</td>
<td>2 900</td>
<td>3 520 000</td>
<td>29 000</td>
</tr>
<tr>
<td>D (Note 2)</td>
<td>3 520 000</td>
<td>29 000</td>
<td>not defined (Note 4)</td>
<td>not defined (Note 4)</td>
</tr>
</tbody>
</table>

Notes:
1. Unidirectional airflow systems provide a homogeneous air speed of 0.45 meters/second +/- 20% (guidance value) at the working position in open clean room applications. The maintenance of unidirectional air flow should be demonstrated and validated. A unidirectional air flow and lower velocities may be used in closed isolators and glove boxes.
2. In order to attain air Grades B, C, and D, the number of air changes will be related to the size of the area and to the equipment and personnel present in the area.
3. Low values for contaminants are reliable only when a large number of air samples are taken. Adequate data is available to generate confidence that the required conditions are met throughout the duration of the operations.
4. The requirement and limits for this area will depend on the nature of the operations carried out.
5. The particulate conditions given in the "at rest" column are to be achieved after a short cleanup period (15 to 20 minutes) in an unmanned state after completion of operations.

The level of risk associated with compounding pharmaceuticals is the key factor in determining the level of oversight required to prevent contamination of the products.

According to USP<797> ‘Low-risk compounding involves only transfer, measuring, and mixing manipulations using not more than three commercially manufactured packages of sterile products and not more than two entries into any one sterile container or package (e.g., bag, vial) of sterile product or administration container/device to prepare the CSP.’ Low-risk compounding applies to radiopharmaceutical CSPs that are compounded according to the manufacturer’s

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2 Good Manufacturing Practices (GMP) 2009, Guidelines, Health Canada Health Products & Food Branch Inspectorate
directions and meet quality assurance requirements and environmental controls. Routine preparation of $^{99m}$Tc-radiopharmaceuticals, according to the supplier’s directions, exemplifies low-risk level activity, provided they are prepared by qualified personnel in a Grade A environment (ISO Class 5; Class 100) laminar-air flow workbench (LAFW) or compounding aseptic isolator (CAI) that is located in a Grade D (ISO Class 8; Class 100,000) buffer area, or a segregated compounding area. Generator systems for $^{99m}$Tc must be eluted according to applicable regulations and use instruction, and the elution process must be done in a Grade D environment. Compliance with these requirements also means that the specified preservative cover for the elution needles must be in place during the shelf life of a generator.

Medium risk compounding of radiopharmaceuticals includes those products where multiple small doses of sterile products are combined to prepare a CSP that will be administered to multiple patients. Procedures such as red cell labeling fall into this category.

An example of high risk sterile compounding of radiopharmaceuticals is the labeling of white blood cells, as this requires manipulations of the product in an open environment. As such, it must be segregated from other radiopharmacy functions and performed in a laminar air flow environment.

Radiopharmaceuticals prepared on an open bench in a non-classified environment would be considered ‘immediate-use CSPs’ as per the Society of Nuclear Medicine Frequently Asked Questions about USP<797> (http://www.snm.org/index.cfm?PageID=7906):

“Most kits may be prepared with $^{99m}$Tc under the immediate-use exemption, with the requirements that the $^{99m}$Tc kit product be administered within 1 hour, any remaining $^{99m}$Tc kit product be discarded, and any remaining $^{99m}$Tc-sodium pertechnetate in the original vial be discarded. Compounding activities falling under the immediate-use exemption do not require clean room facilities, gowning, sterile gloving, masking, etc.”

At this time the preparation of PET radiopharmaceuticals is considered an Establishment Licence activity in Canada i.e. PET radiopharmaceutical production falls under GMP guidelines, rather than compounding. The USP does cover PET under USP <823> ‘Radiopharmaceuticals for Positron Emission Tomography—Compounding’ which supersedes USP<797>. Use of a multi-dose vial of a PET tracer prepared and dispensed in a Grade A environment would need to have a 6-hour expiry after first dispensing according to USP<797>.

The following table provides a summary of risk classifications for pharmaceutical compounding.
Environmental control monitoring includes testing for viable and non-viable particulates routinely, and airflow monitoring in controlled areas.

All personnel responsible for preparing radiopharmaceuticals must have demonstrated that they have appropriate training, and all training is documented. Media fill validation is recommended to evaluate the aseptic technique for all

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personnel. Details regarding the gowning and garbing requirements are provided. A sanitation and disinfection program must be in place.
UNITED STATES PERSPECTIVE ON USP<797> AND COMPOUNDING OF RADIOPHARMACEUTICALS

The historical perspective on the development of USP<797> has been nicely encapsulated in a continuing education document developed by Cooper et al. Briefly, the development and subsequent enforcement of USP<797> in 2004 rose out of increasing reports of contaminated sterile, injectable drug products in the US. The causes of contamination were due to improper aseptic technique and poor environmental control in the compounding area i.e. the facilities were non-compliant with guidelines for the preparation of sterile infusions and medications. One incident involved the contamination with Hepatitis C of a $^{99m}$Tc-labeled cardiac agent, leading to the death of one patient, chronic disease in 12 others, and permanent closure of the nuclear pharmacy. These incidences have resulted in heightened public awareness of compounding pharmacy practice and have led to further regulatory oversight.

In United States, the FDA yields regulatory authority over manufacturers, but not pharmacies: pharmacy regulations are the responsibility of each State. USP<797> falls under federal authority but each State can choose the level of implementation through its own regulations. Therefore FDA has limited authority to enforce USP<797> and relies on the individual States to ensure compliance.

Adoption in the US
The National Association of Boards of Pharmacy has shown support of the USP<797> by incorporating the requirements into its Model State Pharmacy Act and Model Rules. Specific requirements are in “Rules for Sterile Compounding” outlined in the Model State Pharmacy Act. The Board’s Good Compounding Practices Applicable to State Licensed Pharmacies and the current USP-NF chapters on compounding and sterile pharmaceutical preparations are the other requirements for compounding pharmacies and pharmacists.4

Individual states vary in the positions they have taken with respect to USP<797>. Some states have adopted the chapter in its entirety, while most have chosen to incorporate portions of the chapter into laws or regulations. Other states have not made regulatory changes, but instead developed official policies and procedures. A few states have taken no definitive action in terms of written changes to state statutes.5 Implementation has gone through a number of phases, and challenges and feedback from implementation have led to modifications and revisions to the USP compendia’s requirements/recommendations. A certain extent of clarity, consistency and flexibility was introduced e.g. in the $^{99}$Mo/$^{99m}$Tc generator handling environment and the classifications of risk levels.

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4 The ASHP Discussion Guide on USP Chapter <797> for Compounding Sterile Preparations: Summary of Revisions to USP Chapter <797>. Developed by the American Society of Health-System Pharmacists in collaboration with Baxter Healthcare Corporation

Practices Covered by USP<797>:

- Generally, it is stipulated that the USP<797> is intended to apply to all places where compounded sterile preparations (CSPs) are prepared, including hospitals and other healthcare institutions, patient treatment clinics, pharmacies and nuclear pharmacies, physicians’ practice facilities, etc. These standards do apply to nuclear medicine “hot labs”.
- Radiopharmacies are responsible for the proper usage and storage of products post-compounding and up to injection into the patient.
- USP <823> “Radiopharmaceuticals for Positron Emission Tomography – Compounding” supersedes USP<797> for PET radiopharmaceuticals. However, upon release of a PER as a finished drug product from a production facility, the further handling, manipulation, or use of the product is considered compounding, thus USP becomes applicable.
- The preparation of PET drugs, under USP Chapter <823>, and other radiotracers from non-sterile components is considered to be at the high contamination risk level.
- Environmental requirements are exempted for “immediate use” compounding, which may include Rb-82 generator elution, but aseptic technique is an expected performance behavior.
- The USP recognizes that that for radiopharmaceuticals as CSPs, procedures shall respect the “as low as reasonably achievable (ALARA) principle in limiting acute and chronic radioactivity exposure.

Specific Scenarios Highlighted from USP<797> and U.S. Experiences

- $^{99}\text{Mo}/^{99m}\text{Tc}$ generator systems shall be eluted in a Grade D (ISO Class 8) or cleaner air environment. However, it is possible to place a molybdenum-99/technetium-99m generator within an Grade A (ISO Class 5) biosafety cabinet and not require the construction of an Grade D buffer and ante area if compounding is done under the “low-risk CSP standards with a 12-hour or less beyond-use date (BUD) criteria”.
- Most nuclear medicine compounding procedures can fall under Low Risk level. The significant challenge to this categorization is the number of needle punctures through the vial septum.
- Practices that fall under Low-Risk Level meet the criteria:
  - CSPs compounded from sterile commercial drugs using commercial sterile devices
  - Compounding occurs in Grade A environment at all times
  - Compounding procedures involve only transferring, measuring, and mixing manipulations using not more than 3 sterile products and not more than 2 entries into each sterile container
  - Involves only a few closed-system basic, simple aseptic transfers and manipulations
  - Grade A PEC must be located within an Grade C buffer area

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7 Kate Douglass, Eric S. Kastango, MBA, RPh, Peter Cantor. The 2012 USP<797> Compliance Survey: Measuring Progress
All quality assurance, garbing, and visual inspection release check procedures outlined by USP<797> are followed.

Annual media-fill and other applicable competency testing completed for each person who compounds.

- Radiopharmaceuticals compounded from sterile components in closed sterile containers and with a volume of 100 mL or less for a single-dose injection, or not more than 30 mL taken from a multiple-dose container can be designated to the standards for low-risk level CSPs.

- Practices that fall under Low-Risk Level with 12-hour or Less BUD classification meet the criteria.
  - All procedures required for low-risk level CSPs, except, Grade A PEC does not need to be located within a Grade C buffer area.
  - Preparations must be patient specific, based on a prescriber’s order.
  - Administration must start no later than 12 hours after preparation.
  - Compounding area is segregated from areas including, but not limited to: unsealed windows, high traffic areas, food service, or construction to decrease contamination risk.
  - Sinks should not be adjacent to a Grade A PEC.
  - Meet all quality assurance, garbing, aseptic technique procedures, competencies, and environmental testing outlined in USP<797>.

- **Single-Dose and Multiple-Dose Containers** is a relevant recent section and provides criteria for BUDs of single- and multiple-dose containers.
  - If conditions are less than Grade A, opened or needle-punctured single-dose containers are to be used within 1 hour. If conditions are Grade A or cleaner all single-dose containers may be used for up to 6 hours after needle punctures. All remnants must be discarded. *This part is relevant for instance in red blood labeling procedures in nuclear medicine with the use of stannous kits.*
  - Unless written documentation from the manufacturer specifies alternative dating, multiple-dose containers have a 28-day BUD after needle puncture of the vial diaphragm. *This is significant for those preparations that contain preservatives e.g. benzyl alcohol as the preservative bestows a long BUD on the products.*

The Sterile Compounding Committee is the expert committee of the USP on USP<797>. Extensive responses to public comments are included in the Commentary Section and some of the relevant ones include:

- SCC asserts that the description of low-risk level conditions is clear: “no more than three commercially manufactured sterile products, and no more than three entries into one container package (e.g., IV bag or vial) of the sterile products to make the CSP.”

- The SCC used the word “patients” and purposely omitted categorizing them as humans or animals. The intention is that the Chapter applies to CSPs for humans and animals.

- In response to whether isolators can be operated in an uncontrolled environment if they are validated to provide the required environment they state “The SCC agrees that the isolator manufacturer must provide validation information proving through objective testing that the isolator can maintain an ISO Class 5 air quality in the area in which critical
sites are exposed, including entry and egress of essential materials, when the isolator is located in either an ISO Class 7 or 8 controlled environment or any uncontrolled, unclassified environment. The revised chapter states the conditions that must be met if the isolator is located in an uncontrolled environment and only low-risk level nonhazardous and radiopharmaceutical CSPs pursuant to a physician’s order for a specific patient are prepared."

- The SCC adopted the use of sterile gloves in the chapter after considering published data and recommendations from multiple commenters, and the advisory panel formed to review the section in addition to the existence of evidenced-based science in community standard of practice. The greatest risk of contamination is from touch, so by using sterile gloves this bio-burden is minimized.

- To the question whether the scenario of unstable 4-ingredient admixtures may be prepared by competent staff in a surgical environment as Immediate-Use CSPs. **Response:** Under <797>, these admixtures cannot be prepared as Immediate-Use CSPs. SCC stated that the example describes a medium-risk level CSP.

**Implementation principles and approaches**

Cooper *et al* argues that the least expensive changes required by USP<797> tend to be the most effective in reducing CSP contamination and inaccuracy. They state that training personnel on aseptic technique, hand cleansing and garbing is relatively inexpensive. Personnel evaluation through observation, testing, media-fills, and fingertip sampling is next most important. Monitoring the environment for surface microbial contamination, temperature, and humidity is more expensive but effective. Next most important is a review of primary engineering controls, especially those used to protect personnel and the environment from handling hazardous drugs.

It is clear that for most facilities, remodeling of facilities was necessary (U.S. survey, footnote 7). This is clearly a major expense, in particular because smaller hospitals are generally the less compliant and are the ones in most need of facility upgrades. Due to these expenses, many hospital pharmacies have resorted to outsourcing their sterile production. A U.S. memorandum report was recently released providing information about the extent to which acute-care hospitals used CSPs and purchase them from outside sources in 2012. Most hospitals (86%) purchased sterile-to-sterile- CSPs from at least one out-of-State pharmacy, with 3% using products from 4 or 5 out-of-State pharmacies. Although hospitals took limited steps to ensure the quality of outsources CSPs, 50% of those hospitals surveyed are considering changes to their process of validating the supplier after the numerous reports of contaminated products. It is unknown whether radiopharmaceuticals currently cross State-lines, however oversight of radiopharmaceutical preparation resides under State regulations; therefore the potential for variability in adherence and enforcement of USP<797> exists.
In summary, USP<797> has yet to be implemented in a uniform manner across the United States. However it is likely that more stringent regulations and enforcement will follow in the wake of the compounding pharmacy mishaps.
EUROPEAN PERSPECTIVE ON USP<797> AND COMPOUNGING OF
RADIOPHARMACEUTICALS

In Europe, radiopharmaceuticals are considered a special group of medicines. Therefore, their preparation and use are regulated by a number of EU directives, regulations and rules that have been adopted by member states. The rate of adoption of directives varies between countries and each member state may introduce changes, provided the general scope and limits of each directive are maintained.

The United Kingdom has the strictest regulations with a requirement for compounding in a Grade A environment (i.e. laminar airflow hood (LAF) or pharmaceutical isolator) within an appropriate background room (Grade B for open LAFs, Grade D for closed isolators). The process for enforcement is known as PICS - Pharmaceutical Inspection Cooperation Scheme, where the regulatory agencies attempt to harmonize the inspection of non-commercial facilities (primarily hospitals). Radiopharmacies are granted a 'specials' licence by a Government Agency to prepare radiopharmaceuticals. To receive a licence, one must show that the facilities are GMP compliant, with a suitable quality assurance system, that employees are trained, etc. Once a licence is obtained, there are no further restrictions on the radiopharmaceuticals prepared in the facility.

EU generated guidance and guideline documents are recommendations only, i.e. they are not enforceable. Directives are rules addressed by the EU Commission that are to be translated into the respective national legislation. Finally European Regulations are rules directly applied without the need for national legislation.

The EU has developed guidelines and guidances to assist radiopharmacies to develop safe practices in the aseptic preparation of radiopharmaceuticals. Ultimately each country regulates radiopharmacy practice. A summary of the contents of these documents is provided below.

cGRPP-guidelines (Good Radiopharmacy Practice), version2 March 2007 EANM
Radiopharmacy Committee

This document most closely aligns with USP<797> but from the specific aspect of radiopharmaceutical production using (mostly) licenced products.

Facilities
- Radiopharmaceutical production completely segregated from pharmaceutical production
- Equipment reserved exclusively for radiopharmaceuticals
- Equipment validation
- Anteroom for gowing
- Separate Class A workstation for radiolabeling blood products
Generator and Dose calibrator
- Generator in Class A environment
- Radiopharmaceutical production in LAF within Class D environment

Records
- Product preparation
- Laboratory cleaning and maintenance
- Equipment calibration and maintenance
- Training of personnel
- Transport of radioactive materials
- Product defects and events of non-conformity to SOPs
- Microbiological monitoring

Preparation and process controls
- The elution shield and the shields for vials and syringes must be checked for contamination and cleaned inside and outside before use, preferably with 70% ethanol or isopropyl alcohol.
- The aseptic process has to be validated. New personnel have to be qualified by media fills and all personnel requalified at regular intervals.
- Sterility should be controlled on a random sampling following decay of radioactivity. Products are stored for sufficient decay and sent to an external, validated laboratory for sterility testing.
- Pyrogen or bacterial endotoxin testing of radiopharmaceuticals is not routinely carried out.

Environmental monitoring
- Microbiological testing of the aseptic workstation should be performed periodically. Methods can include using swabs or contact plates for surfaces, and settling plates or dynamic air samplers for air quality.

Limited Detail on
- Microbiological controls
- Maintenance and cleaning

EU Guidelines to Good Manufacturing Practices, Annex 3: Manufacture of Radiopharmaceuticals

The preparation of radiopharmaceuticals in radiopharmacies (hospitals or certain pharmacies), using generators and kits with a marketing authorization or a national licence, is not covered by this guideline, unless covered by national requirement. In general, these guidelines are similar in their requirements as GRPP guidelines.
Guidance on current good radiopharmacy practice (cGRPP) for the small-scale preparation of radiopharmaceuticals

This document is meant as a guidance to Part B of the EANM “Guidelines on Good Radiopharmacy Practice (GRPP)” issued by the Radiopharmacy Committee of the EANM (see www.eanm.org), covering the small-scale “in house” preparation of radiopharmaceuticals which are not kit procedures. This document most closely resembles Health Canada’s Good Manufacturing Practices Guidelines and discusses processes commonly associated with PET radiopharmaceutical production.
CANADIAN PERSPECTIVE ON USP<797> AND COMPOUNDING OF RADIOPHARMACEUTICALS

In 2009, The Canadian Journal of Hospital Pharmacists published the results of a survey assessing sterile compounding practices in Canadian hospitals:

“Various degrees of deviation from the practice recommendations were noted for virtually all areas of the CSHP guidelines and the USP standards. Low levels of compliance were most notable in the areas of facilities and equipment, process validation, and product testing. More than 40% of responding pharmacies reported that they did not have a clean room facility. Higher levels of compliance were noted for policies and procedures, garbing requirements, aseptic technique, and handling of hazardous products”.

The Canadian Society of Hospital Pharmacists (CSHP) is currently preparing a document to address USP<797>. According to the CSHP, a disconnect remains between current standards of practice in the compounding and use of sterile products, and the actual practices of Canadian hospital pharmacies. They question the voluntary nature of current Canadian guidelines, and whether meaningful improvement will occur without the development of enforceable standards. A draft copy for review by stakeholders is anticipated in mid-2013.

Other pharmaceutical specialties and pharmacy colleges have embraced USP<797>. For example, pharmacies specializing in oncology contain policies and procedures for handling hazardous drugs which must be consistent with USP<797> regulations. Compliance with USP<797> is considered best practice for compounded sterile products in Canada.

Nuclear Medicine departments in Canada have demonstrated a long and well-established safety profile in the preparation of radiopharmaceuticals with relatively little regulatory oversight from provincial or regulatory authorities. It is only in the last 10 to 15 years that a much more stringent regulatory burden has been placed on radiopharmaceutical production. Health Canada released a guidance document in 1996 providing guidelines for facilities preparing radiopharmaceuticals. Most, if not all, nuclear medicine departments have incorporated these guidelines in their practice.

Adverse Drug Events
Of the 207 radiopharmaceutical-related adverse reactions reported to Health Canada since 1964, 200 events were associated with 99mTc radiopharmaceuticals and their associated kits (http://www.hc-sc.gc.ca/dhp- mps/medeff/databasdon/index-eng.php). Only 10 events were linked to an injection site reaction, which could reflect a pyrogenic reaction. No events were linked with subsequent infection. Considering the number of institutions practicing

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Guidelines for Radiopharmaceutical Quality Assurance in Nuclear Medicine
nuclear medicine in Canada, the number of adverse events is very low. Such low numbers can be attributed to well-trained, qualified personnel. Persons preparing radiopharmaceuticals are either nuclear medicine technologists educated by an accredited technical institution and require a licence to practice nuclear medicine technology; or persons with education in health sciences from an accredited university.

Although past history does not preclude the possibility of a future adverse event, implementation of USP<797> in its entirety would not reduce the risk of an event to zero, and would add significant costs to the healthcare system. Regardless, implementation of certain elements of USP<797> should be considered by all institutions to improve their safety profile, if it can be implemented in a cost-effective manner.

**Issues with USP<797> Implementation in Canada**

**Physical Infrastructure**
The key obstacle in the implementation of USP<797> in nuclear medicine departments is infrastructure. Most hot labs in nuclear medicine departments were designed and built before USP<797> became an official regulation in 2004. Hot labs were designed to comply with CNSC regulations and protect personnel from the ‘product’. All hot labs contain a fume hood for the storage and handling of volatile radioactive materials, such as radioiodine. It is the fume hoods that typically ensure the negative air pressure differential between the hot lab and surrounding area as required by the CNSC. Most hot labs have one or more sinks. These departments have no advanced air filtration, nor minimum requirements for air exchange: the fume hoods are monitored periodically, however, to ensure an appropriate airflow is maintained. In contrast, USP<797> is written with the aim of protecting the product from the personnel. The minimum requirement to prepare low risk CSPs (most 99mTc-radiopharmaceuticals) is within a Grade A environment using a primary engineering control (PEC) such as a Class II, Type A2 or B2 biological cabinet, or a compounding aseptic isolator (CAI). The PEC is housed in an area designated as a segregated compounding area in a Class D classified room. Positive air pressure is generated within the PEC, while the room itself maintains negative pressure differential. For medium-risk CSPs, such as cell labeling procedures, a biological cabinet is surrounded by a Grade C buffer area.

In order to comply with USP<797>, renovation of the room air handling system would be required with the installation of a HEPA filtration system. As well, biological cabinets would be required for each workstation, ideally each with its own dose calibrator. Sinks may need to be moved. The costs for renovation would vary depending on the age and size of the existing labs and department, and impact adjacent rooms or departments with infrastructure costs. Hot labs are invariably located on the ground floor or basement of a facility. Extensive renovation may be required, not only of the hot lab but also the ducts transecting a number of floors above the lab.
The costs for such renovations are not insignificant. For example, a renovation to upgrade a small cleanroom to GMP standards for the production of nonradioactive radiopharmaceutical kits was recently undertaken in a healthcare institute in Alberta. The renovation included a Grade C clean room and anteroom, with an adjoining change room: total area 20.1 sq. m (216 sq. ft.). The total cost for renovation amounted to $210,000, or approximately $10,500 per sq. m ($970/sq. ft.). Assuming that the cost to upgrade a small hot lab to a Grade D environment is similar, the infrastructure costs could amount to $150,000 and substantially more if major ductwork changes are necessary. Assuming 80 such departments in Canada require renovations the estimated cost of the infrastructure alone to healthcare in Canada is $12M. For many institutions no other option exists if nuclear medicine services are to be offered. This is particularly true for rural institutions that have no access to a commercial radiopharmacy operation.

For those institutions that do have access to a commercial radiopharmaceutical vendor, the outsourcing of radiopharmaceuticals may appear as a more attractive alternative. This places the responsibility for sterile radiopharmaceutical production on the centralized radiopharmacy. Although centralized radiopharmacies are subject to GMP guidelines with routine surveillance by the Health Canada Inspectorate, these facilities must be mindful that increased vigilance to environmental and personnel monitoring may be required due to increasingly risk-averse legislators and public. GAP analyses indicate that commercial radiopharmacies generally comply with the infrastructure requirements of both GMP and USP<797>, that is, radiopharmaceuticals are prepared in a PEC within a Grade D (or better) environment. The main challenge lies in the environmental monitoring of these facilities (e.g. volumetric air sampling), and development of SOPs covering radiopharmaceutical compounding practices.

**Capital Equipment**

The Society of Nuclear Medicine Government Relations committee released a document of Frequently Asked Questions (FAQs) about USP<797> with specific questions regarding the handling, or use of radiopharmaceuticals and adjunct drugs (http://www.snm.org/index.cfm?PageID=7906). Essentially every aspect of handling radiopharmaceuticals, from preparation to drawing doses falls under USP<797>. Even drawing a dose of dipyridamole or stannous pyrophosphate would fall under the ‘immediate use’ category. Except for multiple-dose vials containing a preservative, such as [201Tl]Thallous chloride, all doses would be drawn within a PEC in a segregated compounding area, away from the traffic of the department. Based on this interpretation, the purchase of at least one PEC would be required per nuclear medicine department. Installation of biosafety cabinets adds an additional $10,000-$100,000 as a one-time cost to the cost of upgrading the hot lab. Dose calibrator chamber inserts are additional costs. A CAI may be a less expensive
option for smaller and less busy departments. Costs of USP<797> compliant CAIs range between $4500 and $5500.

For monitoring the air pressure differential, a pressure gauge or velocity meter is recommended in USP<797> to measure the differential between the classified and unclassified environments. The most sensitive meters are those that can be connected to existing air monitoring units within the facility for continuous monitoring. The cost to install electronic meters would only be a viable option if the department opted to renovate the hot lab to comply with USP<797>. A magnehelic gauge could be considered, however these units may not be sufficiently sensitive to record the pressure differential between two adjacent areas.

**Personnel Training and Evaluation**

Just as the simple washing of hands prevents many types of ailments, so the practice of good aseptic technique reduces the risk of contaminating sterile products for injection. The low number of adverse events in the past 50 years can attest to good laboratory practices in Nuclear Medicine. Attention to good laboratory technique is critical in the handling of radioactive materials: personnel must be constantly aware of the potential to contaminate the work environment with radioactivity. Therefore, training in handling radioactive materials responsibly lends also promotes good aseptic technique.

USP<797> generally provides good guidance for aseptic technique as per gowning, gloving, as well as the validation of aseptic technique. This aspect of USP<797> should be embraced to as full an extent as possible by all departments/facilities, which prepare radiopharmaceuticals. The purpose is to reduce the microbial and particulate burden to which the radiopharmaceutical is potentially exposed. Aerobic bacterial counts on human skin are in the range of 10⁴-to-10⁶ colony forming units/cm², and squamous cells are shed at a rate of 10⁶ or more per hour.

**Gowning/Garbing Practices**

The best way to reduce numbers of viable and non-viable particulates in the environment is to don low-particulate sterile gowns. Proper technique in gowning and gloving can be provided internally in all public health care institutions through departments such as Infection, Prevention, and Control, or Pharmacy i.e. personnel qualified in aseptic technique.

**Competency Evaluation**

According to USP<797>, expert personnel must train employees in the theoretical principles and practical skills of garbing procedures and aseptic work practices while maintaining Grade D environmental conditions. Competency evaluation includes media fill testing of aseptic work skills and glove fingertip sampling annually. For nuclear medicine departments located within a hospital, expert personnel in infection prevention and control should be utilized to assist in the implementation of media fill validation protocols and evaluation of aseptic technique. Incubation of the media can be performed using internal laboratory
services, or a small incubator can be purchased. Expert external advice may be needed if more cost effective internal resources are not available. Additional staffing, resources and their funding are needed for training and monitoring of personnel.

Environmental Monitoring

Environmental monitoring, such as the routine use of settling plates to monitor for viable particulates, could be readily implemented in a public institution, regardless of whether products are prepared on an open bench or in a PEC. Monitoring open bench practice with settling plates gives personnel an idea of the ‘usual’ microbial burden in the room i.e. it sets a baseline. The effectiveness of the cleaning protocols surface cleaning also requires monitoring through surface sampling methods (swabs or contact plates). Excursions above and beyond the normal microbial count can then be detected and action taken. Laboratory services can monitor for growth and provide detail of microbial colonies. Monitoring of non-viable particulates can be performed routinely either by purchasing a particle counter, or the services can be purchased through a 3rd party and performed twice annually. The financial impact of environmental monitoring will vary. Generally there is wide spread access to laboratory services, however the cost for services will vary regionally and depends on whether services can be accessed internally or provided through 3rd party (as would be the case for private nuclear medicine practices and commercial radiopharmacies).

Financial Impact

Although technically achievable, small hospital departments would require considerable infrastructure upgrades to accommodate the requirements listed in USP<797>. Given the current budgetary restrictions in public healthcare institutions, many departments will choose to outsource radiopharmacy services. Outsourcing has its disadvantages: most centralized radiopharmacies offer unit dose services, which is more costly than preparation of products in-house. As well, the unit dose system does not allow for flexibility of injection times9, and interferes with the department’s ability to provide emergency services. The increased cost can lead to a reduction in imaging services and increase wait times for access to imaging.

The privately operated nuclear medicine imaging clinics are in a unique situation: they do not have access to government funding for infrastructure, and cannot afford extensive upgrades. Some clinics do not have access to centralized radiopharmacy services. For these clinics, the effect could be absolute: the clinics would close if strict adherence to USP<797> was required. This would drive the patient population to hospital departments and, again, increase wait times for nuclear imaging.

9 the ability to titer doses to a patient’s weight is lost with unit doses unless all doses are drawn the morbidly obese patient. This would lead to wasted 99mTc. The alternate situation is that a suboptimal dose is activity is available for injection. Both situations result in an increase in the cost per procedure.
medicine procedures. This would most severely affect myocardial perfusion imaging.

Aside from the impact from the renovation of existing hot labs and the purchase of capital equipment, the ability to absorb the cost of training and competency evaluation will vary from site to site. For nuclear medicine departments within hospitals, the establishment of expertise is essential to develop protocols, and train and monitor personnel in gowning, aseptic technique, and environmental monitoring. Private nuclear medicine practices and commercial radiopharmacies must source these services from a 3rd party, as well as purchase gowns, consumables such as media and agar contact plates, and contract laundering, laboratory, and air monitoring services. These additional services further drive up the cost of the nuclear medicine procedures and ultimately increase the cost to provide diagnostic services. The financial impact will be most keenly felt by private nuclear medicine practices.
RECOMMENDATIONS OF THE CARS USP<797> TASK FORCE FOR RADIOPHARMACEUTICALS IN CANADA

The most serious blockade toward implementation of USP<797> in Canadian nuclear medicine departments is infrastructure costs. Adoption of USP<797> in its entirety would result in a significant increase in the cost of delivery of nuclear medicine services ultimately increasing provincial healthcare costs, reducing access, and increasing wait times for procedures. Regardless, compliance with USP<797> is considered best practice for preparation of compounded sterile products in Canada, and implementation of certain elements of USP<797> should be considered by all institutions to improve their safety profile if it can be implemented in a cost-effective manner. CARS has the expertise to assist nuclear medicine departments and radiopharmacy centres in developing standards and protocols that address the risks associated in the preparation of CSPs as they pertain to radiopharmaceuticals. The benefit to CARS is that it raises its profile within the nuclear medicine community, by acting as a conduit for information and providing guidance to the community.

CARS USP<797> Task Force Recommendations

CARS should lead, or be a major player and active participant in the development of guidance/regulatory documents that affect the practice of radiopharmacy. CARS must be given timely access to any guidelines developed by federal, provincial, or professional pharmaceutical associations that affect radiopharmaceutical preparation.

CARS USP<797> Task Force recommendations are as follows:

1. All radiopharmacies and nuclear medicine departments should move towards implementing aspects of USP<797> whenever feasible within current constraints of facility design, resources and budgets. Hospital/facility executives must be alerted to the potential necessity of infrastructure changes, staffing, training, and budget that may be necessary for compliance.

2. All requirements outlined in USP<797>, including but not limited to infrastructure, must be considered in the development of any new facility or upgrade of a facility that intends to prepare and/or dispense radiopharmaceuticals.

3. A CARS committee shall assess any new policies, procedures, or documents related to preparation of radiopharmaceuticals in Canada and, if necessary, prepare guidelines to ensure radiopharmaceuticals continue to be prepared in a safe and efficacious manner with due consideration to radiation safety and radiopharmaceutical quality assurance.

4. Each nuclear medicine department and radiopharmacy is encouraged to prepare a risk assessment analysis (GAP analysis) to categorize current compliance level, identify gaps in compliance, develop a remedial strategy, quantify required budgets and resources (e.g. training and personnel), and prioritize an action plan. Use of an external expert or consultant may be necessary if expertise does not exist locally. A template for
performing an analysis is available from the American Society of Health System Pharmacists

5. CARS and other stakeholders should perform a survey of Radiopharmacy and Nuclear Medicine practices to obtain information of the perceived challenges for compliance.

6. CARS should develop electronic resources (website, etc) for dissemination of information and/or provide relevant links to documents/protocols. Website content could include:
   - Check list for GAP analysis
   - Standard operating procedures that can be used as a template for each institution to develop its own protocols covering methodology for
     - media fill validation
     - environmental and personnel monitoring
     - gowning/garbing practices
     - disinfecting/cleaning
     - teaching/training
   - A list of 3rd party service providers across Canada that provide training and perform environmental monitoring.
   - A panel of experts to assist with specific <USP> 797 issues

**Disclaimer**
This document does not address every issue within USP<797> but only those most relevant to the practice of Radiopharmacy and Nuclear Medicine. Further analysis of the impact of USP<797> may be required to ensure that all aspects of this document are considered.
BIBLIOGRAPHY


Canadian Association of Pharmacy in Oncology (CAPhO). Standards of Practice for Oncology Pharmacy in Canada, Version 2, November 2009.