CONSIDERATIONS RELATED TO PRODUCTION OF RADIOPHARMACEUTICALS IN AUSTRALIA

A PRIMER FOR MEMBERS

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1. EXECUTIVE SUMMARY

Molecular imaging and radionuclide therapy using radiopharmaceuticals has great potential in the current move toward a more personalised approach to patient management. This potential is already starting to be realised via patient access to unapproved, extemporaneously compounded radiopharmaceuticals such as [^{68}Ga]Ga-HBED-CC-PSMA. Due to economic and/or pragmatic factors such as low patient numbers, or low production activities in combination with short half-life and/or shelf-life, some of these compounded products will not be available to nuclear medicine clinics through commercial suppliers (*e.g.*, centralised radiopharmacies). Therefore, "in-house" preparation of these products will become increasingly necessary for patient access.

Australia has witnessed substantial recent growth in the number of PET/CT imaging facilities conducting in-house preparation of PET radiopharmaceuticals, driven primarily by the success of new ^{68}Ga- and ^{177}Lu-labelled radiopharmaceuticals, as well as the availability of ^{68}Ge/^{68}Ga generators and easy-to-use commercially available automated synthesis solutions. With the growing pressure for in-house production comes an increased risk of misdiagnosis, ineffective therapy, and the potential for an adverse reaction if Good Radiopharmacy Practices are not followed. As the primary provider of scientific and peer support for the nuclear medicine community, the Australian and New Zealand Society of Nuclear Medicine (ANZSNM) formed a working party to review issues surrounding the in-house production of radiopharmaceuticals.

Important in the discussion about in-house production is the recognition that radiopharmaceuticals are considered a medicine when produced in-house in Australia, and must comply with the requirements of the Therapeutic Goods Act 1989 ("the Act"), even when manufactured under exemptions provided for in the Therapeutic Goods Regulations ("the Regulations").

This report summarises the Federal Laws and Regulations governing the manufacture of medicinal products in Australia and their applicability to in-house production. New Zealand legislation was not reviewed in this investigation and may be considered as a potential follow-up project to aid the New Zealand Branch. Specific findings of this review are summarised below:

- Exemptions to the requirements for medicines to be registered and manufactured in Therapeutic Goods Administration (TGA) licensed facilities exist in the legislation and these allow Australian nuclear medicine clinics to conduct in-house manufacture of unapproved radiopharmaceuticals for administration to their patients;
- Sites seeking to conduct in-house preparation of radiopharmaceuticals should:
  - Document the legal basis by which they will conduct their activities, including listing and providing justification for the specific exemptions applied;
  - Document their risk management process, their assessment of risk as well as the effectiveness of any mitigating strategies. This should include reviewing practices against international standards of Good Radiopharmacy Practice such as those published by the EANM and in the pharmacopoeias;
  - When considering risks, sites should keep in mind that the Therapeutic Goods Act and Regulations have not yet been legally contested both in the interpretation of exemptions and their application to the in-house production of radiopharmaceuticals.

2. CURRENT REGULATIONS AND GUIDELINES

Key Question: *What are the current regulatory requirements for in-house production of radiopharmaceutical compounds in Australia?*

2.1 Australian Legislative Framework

The major legislation dealing with regulation of therapeutic goods (such as radiopharmaceutical medicines) in Australia is the *Therapeutic Goods Act 1989* (the Act)[1] and the *Therapeutic Goods Regulations 1990* (the Regulations)[2]. The Objects of the Act (s4(1)(a)) and associated Regulations include to "*provide for the establishment and maintenance of a national system of controls to ensure the quality, safety, efficacy and timely availability of therapeutic goods*". Responsibility for the regulatory controls lies with the Therapeutic Goods Administration (TGA) as the national regulatory authority for therapeutic goods.

According to the legislation, medicines supplied in Australia for human use that are imported, manufactured in Australia, supplied by a corporation, supplied interstate or to the Commonwealth, or exported, are required to be:

(a) approved and included on the Australian Register of Therapeutic Goods (ARTG) before they can be supplied, unless specifically exempted under the legislation (Part 3-2 of the Act "Registration and listing of therapeutic goods"); and

(b) manufactured by persons licensed to manufacture at licensed premises (i.e. manufactured according to the Code of Good Manufacturing Practice [GMP] at a TGA licensed facility) unless an exemption under the legislation applies (Part 3-3 of the Act "Manufacturing of therapeutic goods").

2.1.1 Criminal and Civil Offences

It is a criminal offence (s19B) to manufacture and/or supplying medicines for human use in Australia that are not registered goods in relation to the person and the use of the goods (i) *has* resulted in, or *will* result in, or (ii) if the goods were used *would* result in, harm or injury to any person. This renders the person liable to penalties (including possible imprisonment for 5 years) unless an exemption is granted or exists under the Regulations. It is also an offence to manufacture and/or supply unregistered medicines for human use where no exemption in relation to the goods exists, and the use of the goods, if the goods were used, would be *likely* to result in harm or injury to any person.

Likewise, it is a criminal offence (s35) to manufacture therapeutic goods for human use without a TGA licence. This renders the person liable to penalties unless the goods are exempt goods (see examples in Table 3 below), or the person is an exempt person (see examples in Table 4 below) in relation to the manufacture of the goods.

The promotion of unapproved medicines is an offence (s22(6)) and carries a financial penalty. A person must not intentionally or recklessly make a claim, by any means, that the person or another person can arrange the supply of unapproved therapeutic goods.

2.1.2 States & Territories

Under the Act, the TGA is able to release information concerning the use of unapproved therapeutic goods to State and Territory bodies that have functions relating to therapeutic goods or that are responsible for the regulation of medical practitioners or pharmacists. This allows States and Territories to access information to take action on matters under

their jurisdiction, such as medical or pharmacy practice. The circumstances under which this may occur include, but are not limited to, the TGA becoming aware that a medical practitioner is using notification mechanisms (e.g. SAS Category A) inappropriately, so as to avoid having to obtain approval from the TGA for supply of an unapproved therapeutic good.

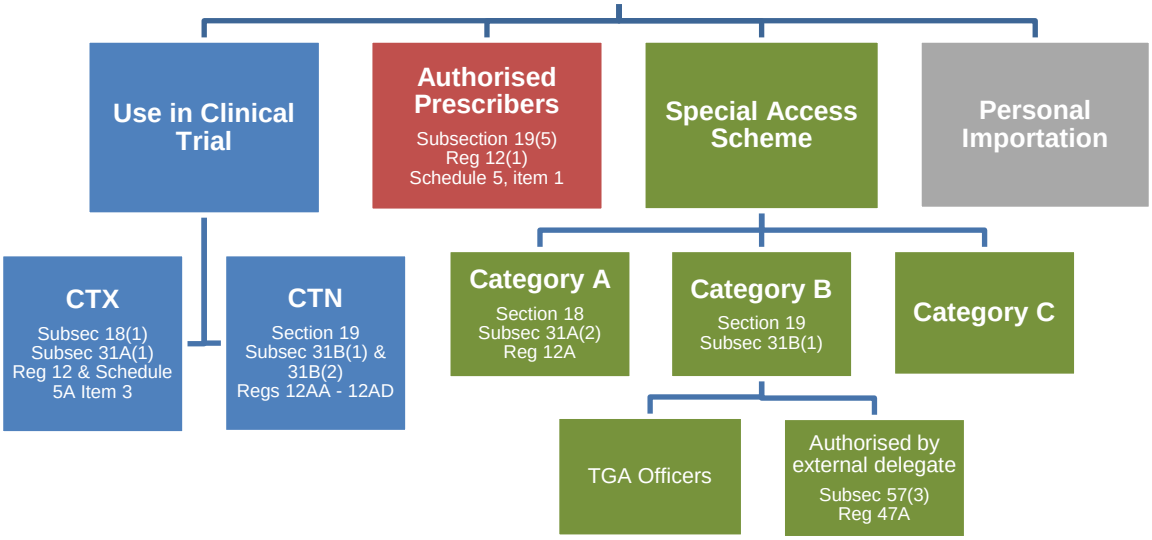
This report has not investigated the differences in State and Territory legislation and how this impacts on in-house manufacture of radiopharmaceuticals.

2.2 Access to unapproved therapeutic goods

Some therapeutic goods are exempt under the Act (s18-19) from the requirement for inclusion in the ARTG (Part 3-2 of the Act) before they can be supplied. Figure 1 shows four mechanisms available under the legislation by which an individual may gain access to unapproved radiopharmaceuticals:

- Special Access Scheme (categories A, B and C)[3]
- Clinical Trials (CTN and CTX schemes)[4]
- Authorised Prescribers[5]; and
- Importation for personal use[6].

Figure 1: Access to unapproved medicines and other therapeutic goods (OTGs)



2.2.1 Clinical Trials

Clinical Trials are a common mechanism by which individuals gain access to unapproved radiopharmaceuticals to assess the investigational product's safety and/or clinical usefulness in imaging or therapy. Historically, these investigations have been undertaken in nuclear medicine departments of major academic teaching hospitals.

The TGA have published "The Australian Clinical Trials Handbook" to provide guidance on the legislative, regulatory, and Good Clinical Practice (GCP) requirements when conducting clinical trials in Australia of 'unapproved' therapeutic goods.[4]

There are two routes for conducting a clinical trial of new therapeutic goods or new uses of existing therapeutic goods:

- the Clinical Trial Notification (CTN) Scheme; and
- the Clinical Trial Exemption Scheme (CTX Scheme).

Under the CTN Scheme, the trial protocol is not approved by the TGA, but by the institution or organisation at which the trial will be conducted, having due regard to advice from the Human Research Ethics Committee (HREC).

Under the CTX Scheme, the sponsor submits an application to conduct clinical trials to the TGA for evaluation and comment.

The primary responsibility for monitoring a clinical trial rests with the sponsor, the institution in which the trial is being conducted and the institution's HREC, and the principal investigator.

2.2.2 Special Access Scheme (SAS)

The SAS refers to arrangements for the import and/or supply of an unapproved therapeutic good for a single patient on a case by case basis. Historically, there were two pathways for accessing unapproved medicines, designated Category A and Category B. Recently, the Australian government accepted the Expert Review of Medicines and Medical Devices Regulation recommendation to enable faster patient access to unapproved therapeutic goods that are deemed to have an established history of use by not requiring that these goods be approved by the TGA before they can be accessed. In response, Category C was established.[3]

- Category A is a **notification** pathway which can be accessed by health practitioners on behalf of a prescribing medical practitioner for patients who are seriously ill with a condition from which death is reasonably likely to occur within a matter of months, or from which premature death is reasonably likely to occur in the absence of early treatment.
- Category B is an **application** pathway which can be accessed by health practitioners for patients who do not fit the Category A definition and where the unapproved therapeutic good is not eligible under Category C of the Therapeutic Goods Administration Special Access Scheme (SAS)[3] An approval letter from the TGA is required before the good may be accessed under Category B.
- Category C is a **notification** pathway which allows health practitioners to supply goods that are deemed to have an established history of use without first seeking prior approval. The goods deemed to have an established history of use are specified in a list along with their indications and the type of health practitioner authorised to supply these products for their respective indications. Of particular interest to the ANZSNM, are the following unapproved medicines on the current list (Table 1):[7]

Table 1: *Select unapproved medicines of interest to ANZSNM that qualify for the SAS Category C*

Specified therapeutic goods				
Column 1	**Column 2**	**Column 3**	**Column 4**	**Column 5**
Item	**Active ingredient**	**Dosage form**	**Route of administration**	**Indication**
25	F-18 myocardial perfusion tracer (18F flurpiridaz)	injection	intravenous	myocardial perfusion study
26	F-18 NaF (sodium fluoride)	injection	intravenous	bone study
30	Gallium-68 (Ga-68) Galligas	aerosol	inhalation	lung ventilation study
31	Gallium-68 (Ga-68) - MAA	injection	intravenous	lung perfusion study
78	Yttrium-90 (Y-90) Citrate	injection	intraarticular	radiosynovectomy treatment

2.2.3 Authorised Prescriber

The TGA is able to grant certain medical practitioners authority to prescribe a specified unapproved therapeutic good or class of therapeutic goods to specified recipients or classes of recipients (as identified by their medical condition). The medical practitioner becomes an 'Authorised Prescriber' and can prescribe the product for that specific condition to individual patients in their immediate care without further approval from the TGA.

2.2.4 Personal Importation

This access mechanism is not in scope of the in-house production of radiopharmaceuticals so will not be explored further.

2.2.5 Relevant Therapeutic Goods Exempt from Part 3-2 of the Act

Particular classes or types of therapeutic goods are exempt from the requirement to be entered into the Australian Register of Therapeutic Goods (ARTG). These are detailed in Schedule 5 of the Regulations. Further exemptions are detailed in Schedule 5A but these exemptions are subject to conditions. Excerpts of Schedule 5 and 5A which are of interest to nuclear medicine are detailed in Table 2 and Table 3.

Table 2: *Excerpts of interest from Schedule 5 (sub-regulation 12(1)): Therapeutic goods exempt from operation of Parts 3-2 and 3-2A of the Act*

Item No.	Therapeutic goods
6	medicines that are dispensed, or extemporaneously compounded, for a particular person for therapeutic application to that person, other than medicines that are used for gene therapy
13	radiopharmaceutical cold kits that are: (a) containers of sterile reagents to which radioisotope is added immediately before injection into patients; and (b) manufactured by a radiochemist or a pharmacist in a public or private hospital for subsequent extemporaneous compounding and dispensing for use by, or in connection with: (i) a patient of that hospital; or (ii) a patient of another public or private hospital in the same State or Territory

Item number 6 in Table 2 refers to standard pharmacy practice and appears to be highly relevant to the small scale in-house preparation of radiopharmaceuticals. To clarify the key terms used in the exemption, Pharmacy Board of Australia's definitions of 'dispensing' and 'extemporaneous compounding' are provided here:[8]

Dispensing:	the preparation, packaging, labelling, record keeping and transfer of a prescription drug to a patient, their agent, or another person who is responsible for the administration of the medicine to that patient
Extemporaneous Compounding:	The preparation and supply of a single 'unit of issue' of a therapeutic product intended for supply for a specific patient in response to an identified need.

In-house preparation of a radiopharmaceutical typically results in a single product vial which may be intended for an individual patient or as a multi-dose vial for dispensing a small number of individual patient doses. For ^{68}Ga-labelled and ^{177}Lu-labelled radiopharmaceuticals, this is typically in the order of 1 to 4 patient doses per in-house batch preparation, with patients regularly administered the dose within 2 hours of preparation. For longer half-life radionuclides such as iodine-131, indium-111, lutetium-177 and zirconium-89, there is scope for product storage over 24 hours before administration, if product stability allows. The product vial typically contains a small excess of radioactivity over the prescribed individual patient dose(s) to ensure adequate radioactivity is administered for the diagnostic or therapeutic purpose of the dose.

Item Number 13 in Table 2 is highly relevant to Nuclear Medicine. This exemption has been applied by radiochemists and radiopharmacists in hospitals for the in-house preparation of sterile 'cold kits' for labelling with technetium-99m. Batches of the cold kits are prepared under clean room conditions and stored until required. This exemption may be of increasing relevance to $^{61/64/67}$Cu-labelled, ^{68}Ga-labelled and ^{177}Lu-labelled radiopharmaceuticals should a shift towards a 'cold kit' approach to the in-house preparation of these radiopharmaceuticals be adopted.

The exempt therapeutic goods in Schedule 5A (see Table 3 below) include experimental products (Item Number 3) which have been discussed in Section 2.2.1 above. Item Number 5 is not particularly relevant to this investigation of in-house production of radiopharmaceuticals as it relates specifically to unique products made under contract by a GMP manufacturer for a public or private hospital. This exemption allows a commercial GMP facility to manufacture radiopharmaceuticals for a public or private hospital without the requirement to register the product on the ARTG, as long as the product manufacture is covered by the Schedule of Conditions on the manufacturer's licence. However, this exemption is not permitted if a registered product exists that in all relevant aspects is substantially similar to the contracted goods.

Table 3: *Excerpts of interest from Schedule 5A (sub-regulations 12(2) and 12(3)): Therapeutic goods exempt from operation of Parts 3-2 and 3-2A of Act subject to conditions*

Item No.	Therapeutic goods	Conditions
3	Therapeutic goods used solely for experimental purposes in humans	(a) before starting to use the goods, the sponsor must notify the Secretary: (i) in a form approved by the Secretary; and (ii) in accordance with the requirements (if any) determined by the Secretary for the form of notification; that the sponsor intends to sponsor a clinical trial using the specified goods; and (b) the notification must be accompanied by the relevant notification fee referred to in item 14 or 14A of Schedule 9 or item 17 of Schedule 9A; and (c) the approval of the goods for this purpose must be given by the sponsor (if the sponsor is conducting the trial), or by the body or organisation conducting the trial for the sponsor, having regard to the advice of the ethics committee that has, or will assume, responsibility for monitoring the conduct of the trial; and (d) the terms of the approval by the sponsor, body or organisation referred to in paragraph (c) must be no less restrictive than the terms advised by the ethics committee; and (e) the Secretary must not, at any time: (i) have become aware that to conduct or continue the trial would be contrary to the public interest; and (ii) have directed that the trial not be conducted, or be stopped; and (f) the sponsor (if the sponsor is conducting the trial), or the body or organisation conducting the trial for the sponsor, must not receive, or have received, advice from the ethics committee that is inconsistent with the continuation of the trial; and (g) the conditions set out in regulation 12AD must be complied with, as if that regulation applied to a person using therapeutic goods under this item; and (h) the goods are not any of the following: (i) a Class 4 biological that has not received clinical trial approval for an equivalent indication from a national regulatory agency with comparable regulatory requirements; (ii) a Class 4 biological that does not have a history of previous usage that is supported by clinical evidence received by the TGA (i) the sponsor must comply with requests by an authorised officer, whether made before or after the start of the trial, to give information about the conduct of the trial (whether or not the sponsor is conducting the trial); and (j) if a body or organisation is conducting the trial for the sponsor, that body or organisation must comply with requests by an authorised officer, whether made before or after the start of the trial, to give information about the conduct of the trial; and (k) the sponsor (if the sponsor is conducting the trial), or the body or organisation conducting the trial for the sponsor, must allow an authorised officer to do the things mentioned in regulation 12AC

5	Therapeutic goods, if: (a) the goods are not: (i) biologicals; or (ii) goods referred to in item 3; and (b) the goods are manufactured by a person under a contract between the person and a private hospital, a public hospital in a State or Territory or a public institution (the ***relevant institution***); and (c) the manufacture is in accordance with a formulation specified by the relevant institution; and (d) the goods are for use by, or in connection with, a patient of: (i) the relevant institution; or (ii) if the relevant institution is a public hospital in a State or Territory—another public hospital in the State or Territory	(a) there are no listed goods or registered goods that, in all relevant aspects, are substantially similar to the goods; and (b) the person: (i) manufacturers the goods at premises in Australia; and (ii) holds a licence, required by the Act, that authorises the manufacture, or a step in the manufacture, of the goods at those premises; and (c) the person notifies the Secretary, in accordance with a form approved by the Secretary and within 15 days of the end of a quarter, of: (i) the goods manufactured under the contract during that quarter; and (ii) the private hospital, public hospital or public institution that entered the contract

2.3 Manufacture and supply of unapproved therapeutic goods

Medicines supplied under the Clinical Trial Notification (CTN) Scheme, Authorised Prescriber (AP) or Special Access Scheme (SAS) are exempt from, or approved/authorised under, Part 3.2 of the *Therapeutic Goods Act 1989* (the Act). That is, they are exempt from the requirement for the medicine to be entered on the Australian Register of Therapeutic Goods (ARTG). However, these exemptions, approvals or authorisations do not extend to Part 3.3 of the Act. Manufacturing of medicines is covered under Part 3.3 of the Act which requires that medicines supplied in Australia must be manufactured by persons licensed to manufacture at licensed premises ***unless an exemption applies*** (emphasis added). In general, a facility manufacturing medicines in Australia must comply with appropriate GMP standards and must be licensed accordingly.

Of particular interest to ANZSNM members in Australia are the following exemptions described in the Regulations, in Schedules 7 and 8.

2.3.1 Exemptions under Schedule 7

Schedule 7, Item 1 of the Regulations (Table 4) provides an exemption to the requirement for a manufacturer to hold a TGA licence when the radiopharmaceutical product in question is being manufactured for initial experimental studies in human volunteers. The term “initial” is generally interpreted to mean Phase I clinical trials.

In response to the sudden decrease in commercial flights within Australia, due to the global novel coronavirus pandemic (COVID-19), the Minister for Health acted to amend Schedule 7 for the purposes of facilitating continued supply of critical radiopharmaceuticals and radiopharmaceutical active ingredients (RAI) in Australia during the pandemic.[9] Two additional exemptions were added to Schedule 7, items 22 (radiopharmaceuticals) and 23 (RAI). The wording of the two emergency exemptions (see Table 4) is similar to the wording of exemption items 1, 2 and 3 in Schedule 8 (see

Section 2.3.2) but with increased scope for supply to any destination in Australia. The two exemptions address the current difficulties in obtaining supplies of radiopharmaceuticals and RAI from a licensed manufacturer in a timely manner during the COVID-19 outbreak. Reflecting the extraordinary circumstances necessitating the new exemptions, the exemptions are to be reviewed as current COVID-19 circumstances change. Accordingly, hospitals or public institutions should not rely on the new exemptions as a long-term option for manufacturing radiopharmaceuticals or RAI without a licence under the Act.[9]

Table 4: *Excerpt of interest from Schedule 7 (Regulation 17): Therapeutic goods exempt from operation of Part 3-3 of the Act unless supplied as pharmaceutical benefits*

Item No.	Therapeutic goods
1	goods prepared for the initial experimental studies in human volunteers
22	radiopharmaceuticals if: (a) the radiopharmaceuticals are manufactured by: (i) a medical practitioner registered under a law of a State or Territory when employed by a public or private hospital or a public institution, or a person under the professional supervision of such a medical practitioner; or (ii) a radiochemist when employed by a public or private hospital or a public institution, or a person under the professional supervision of such a radiochemist; or (iii) a pharmacist registered under a law of a State or Territory when employed by a public or private hospital or a public institution, or a person under the professional supervision of such a pharmacist; and (b) the radiopharmaceuticals are for supply to another public or private hospital, another public institution or a private institution within Australia for the purposes of: (i) diagnosing a medical condition in respect of a patient of the hospital or institution; or (ii) treating a medical condition of a patient of the hospital or institution
23	radiopharmaceutical active ingredients if: (a) the ingredients are manufactured by: (i) a medical practitioner registered under a law of a State or Territory when employed by a public or private hospital or a public institution, or a person under the professional supervision of such a medical practitioner; or (ii) a radiochemist when employed by a public or private hospital or a public institution, or a person under the professional supervision of such a radiochemist; or (iii) a pharmacist registered under a law of a State or Territory when employed by a public or private hospital or a public institution, or a person under the professional supervision of such a pharmacist; and (b) the ingredients are for supply to another public or private hospital, another public institution or a private institution within Australia, which are then used by the hospital or institution to manufacture a radiopharmaceutical for the purposes of: (i) diagnosing a medical condition in respect of a patient of the hospital or institution; or (ii) treating a medical condition of a patient of the hospital or institution

2.3.2 Exemptions under Schedule 8

Schedule 8 details particular healthcare professionals who are exempt from the requirements of Part 3-3 of the Act under specific conditions (see Table 5). Of particular relevance to the in-house preparation of radiopharmaceuticals are:

- Item 1(a) concerning manufacture of a medicine by a medical practitioner for their patient;
- Item 2 concerning manufacture of therapeutic goods by a pharmacist in a private hospital or other qualifying pharmacy; and
- Item 3 concerning manufacture of therapeutic goods by biomedical engineers, pharmacists and radiochemists employed by a public hospital or public institution for local supply to hospitals and institutions in the same State or Territory.

Table 5: *Excerpts of interest from Schedule 8 (Regulation 18): Persons exempt from the operation of Part 3-3 of the Act*

Item No.	Persons	Matter in relation to which person exempted
1	medical practitioners, dentists and other health care workers registered under a law of a State or Territory	the manufacture of: (a) a medicine by a medical practitioner or a dentist specifically for a patient under his or her care; or (b) a therapeutic device by a health care worker specifically for a patients under his or her care
2	pharmacists	the manufacture of therapeutic goods, if: (a) the goods are not biologicals; and (b) the goods are produced by the pharmacist: (i) in a pharmacy where the pharmacist practices and the pharmacy is open to the public; or (ii) on the premises of a dispensary conducted by a Friendly Society; or (iii) on the premises of a private hospital; and (c) the goods are for supply (other than by wholesale) on or from those premises
3	biomedical engineers, radiochemists and pharmacists in public hospitals	The manufacture of therapeutic goods, other than biologicals, by the person when employed by a public hospital or a public institution and produced by that person for supply in hospitals or public institutions in the same State or Territory

Medical Practitioners: In relation to in-house production of radiopharmaceuticals, Item Number 1 states that medical practitioners are exempt from the requirement to hold a TGA licence to manufacture a medicine specifically for a patient under his or her care. However, it is not clear whether this means that the medical practitioner must conduct the manufacture or instead be responsible for the manufacture that takes place under his or her supervision and authorisation. By contrast, the wording of the COVID-19 related temporary exemptions in Schedule 7, items 22 and 23 (see Table 4) is much clearer and specifically allows "a person under the professional supervision of such a medical practitioner".

Pharmacists[10]: Schedule 8, Item 2 exempts pharmacists working in either a community pharmacy or in a private hospital from the requirement to obtain a TGA licence when manufacturing therapeutic goods other than biologicals. The condition specifies it is for direct supply on or from those premises (*i.e.* not wholesale supply). Item Number 3 exempts pharmacists working in a public hospital or public institution from the requirement to manufacture under a TGA licence but is restricted to supply only to hospitals and public institutions within the same State or Territory. Pharmacists are also expected to comply with all relevant professional practice standards and guidelines. The Pharmacy Board of Australia has published *Guidelines on Compounding of Medicines*[8] which specifies the relevant practice standards and guidelines for compounding medicines.

Biomedical Engineers and Radiochemists: Item Number 3 exempts biomedical engineers and radiochemists employed in public hospitals or public institutions from manufacturing therapeutic goods (other than biologicals) under a TGA licence. This is restricted to supply within the same State or Territory. A public institution includes public universities and medical research institutes.

While the term "radiochemist" appears in Schedule 8 of the Regulations, the term does not have a legal definition in a same way a pharmacist does, nor the clearly understood qualifications required for the "engineer" job title in the term "biomedical engineer" also

found in Schedule 8. The interpretation of this term “radiochemist” in the legislation is of particular interest as many sites conduct in-house preparation of radiopharmaceuticals using their complement of Nuclear Medicine Technologists (NMTs) as this workforce has basic training in radiopharmacy. Some NMTs may have also undertaken additional training in radiopharmacy via university or in-house training by an experienced radiopharmacist / radiochemist. “Radiopharmaceutical Scientists” is a professional term that has been embraced by the Australian College of Physical Scientists and Engineers in Medicine (ACPSEM) who are now providing an accredited training pathway and certifying these professionals in a similar way to Medical Physicists. The NSW Government has adopted the ACPSEM definition of a Radiopharmaceutical Scientist (see http://www.health.nsw.gov.au/workforce/alliedhealth/Factsheets/rps-career.pdf). While ACPSEM-certified Radiopharmaceutical Scientists include pharmacists who have specialised in radiopharmacy and voluntarily pursued ACPSEM certification, it is important to note that pharmacists in Australia have national accreditation through AHPRA.

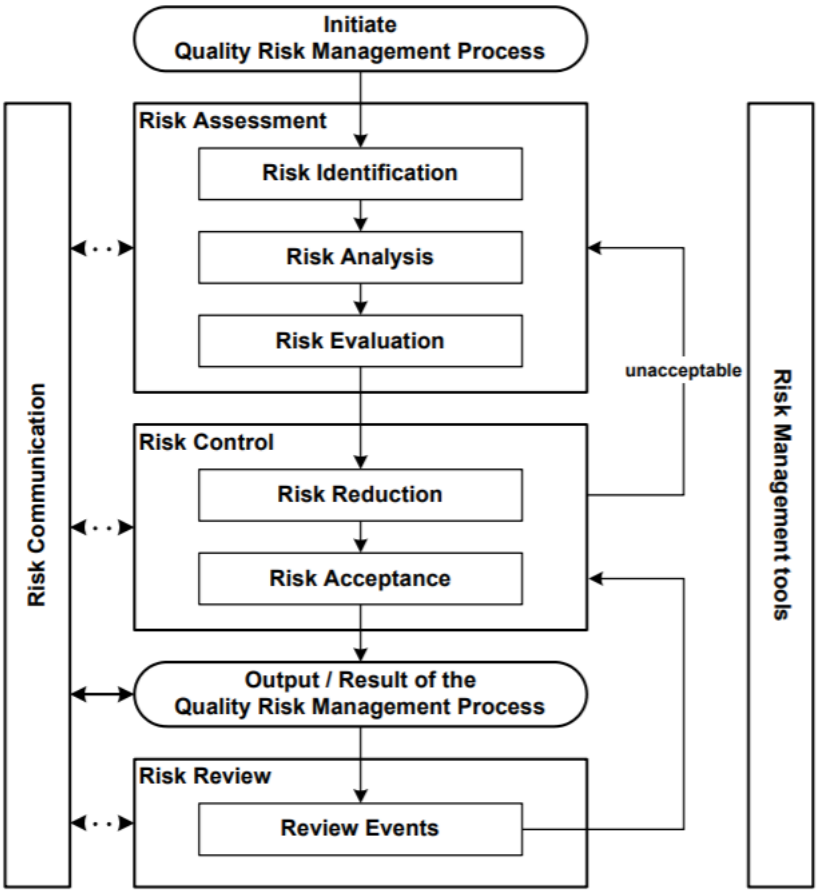
Sections 2.2 and 2.3 above have outlined several relevant exemptions to the requirements of the legislation to manufacture registered radiopharmaceuticals in TGA-licensed facilities. It is important to note that the exemptions detailed above do not exempt in-house manufactured radiopharmaceuticals from meeting the quality standards or advertising requirements set out in the *Therapeutic Goods Act 1989*.

3. RISK MANAGEMENT

In-house preparation of unapproved radiopharmaceuticals affords an opportunity for nuclear medicine departments to improve patient management through precision medicine. While the goal is to improve patient outcomes, in-house preparation is not without risk. Extemporaneously compounded sterile injectable medicines prepared by aseptic filtration are considered by the regulatory authorities as being in the highest risk category of medicine manufacture as the critical quality attribute of sterility cannot be verified prior to patient administration. Short-lived or short shelf-life radiopharmaceuticals have the additional time pressure of verifying other critical quality attributes, such as radiochemical purity, within a short time frame. To mitigate these inherent risks, Good Radiopharmacy Practice (GRPP) must be followed. GRPP is described in the European Pharmacopoeia[11], PIC/S Guide[12] and various guidance documents published by the EANM[13,14,15,16].

Not all in-house production procedures and products carry equivalent risk with regards to safety and efficacy. Sites conducting in-house preparation of radiopharmaceuticals should document their control strategy for each product and process using Quality Risk Management (QRM) principles. An overview of a typical QRM process is shown in the flowchart in Figure 2.[17] The two main principles of QRM are (1) the use of scientific knowledge to evaluate the risk to quality and, ultimately, the link to protection of the patient; and (2) effort, formality and documentation of risk assessment, risk control, and risk management measures, that are commensurate with the level of risk.[17] Such a process would, for example, see a lower risk assigned to a single-step reconstitution of a commercial GMP manufactured sterile cold kit with sterile radionuclide solution for diagnostic imaging purposes, compared to a much higher risk for a diagnostic or therapeutic agent prepared by a complex process using non-GMP grade and/or non-sterile reagents.

Figure 2. Overview of a typical QRM process[17]



4. CONCLUDING REMARKS

This document has summarised the current legal basis for in-house preparation of unapproved radiopharmaceuticals as outlined in the *Therapeutic Goods Act 1989* and the *Therapeutic Goods Regulations 1990*. Specific exemptions to the requirements for medicines to be registered on the ARTG and manufactured in TGA licensed facilities exist in the legislation which, when the conditions are met, permit Australian nuclear medicine clinics to conduct in-house manufacture of unapproved radiopharmaceuticals for administration to their patients. It should be recognised that compounded and dispensed medicines are not exempt from the quality requirements set out in the Therapeutic Goods Act 1989.

The following considerations are for sites seeking to conduct, or already conducting, in-house preparation of radiopharmaceuticals:

1. Sites should document the legal basis by which they will conduct their in-house preparation of radiopharmaceuticals. This should include listing and providing justification for the specific exemptions applied. Sites should also review the requirement for in-house preparation of radiopharmaceuticals when GMP manufactured alternatives become commercially available;

2. Sites should document their risk management process, their assessments and review of specific risks, as well as the effectiveness of any mitigating strategies. Sites should review their practices against international standards of Good Radiopharmacy Practice such as those published by the EANM and in the pharmacopoeias;

3. Sites should recognise that, to the best of knowledge, the *Therapeutic Goods Act* and *Regulations* have not yet been legally contested with regards to their application to the in-house production of radiopharmaceuticals. Ethical issues aside, this may influence the approach to risk management and the investment in equipment, facilities and training.

5. REFERENCES

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6. ACRONYMS

The following acronyms have been adopted in this report.

ACPSEM	Australasian College of Physical Scientists and Engineers in Medicine
AHPRA	Australian Health Practitioner Regulation Agency
ANZSNM	Australian and New Zealand Society of Nuclear Medicine
AP	Authorised Prescriber
ARTG	Australian Register of Therapeutic Goods
CTN	Clinical Trial Notification
CTX	Clinical Trial Exemption
EANM	European Association of Nuclear Medicine
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GRPP	Good Radiopharmacy Practice
HREC	Health Research Ethics Committee
IV	Intravenous
NMT	Nuclear Medicine Technologist or Scientist
OTG	Other Therapeutic Goods
PET	Positron Emission Tomography
PIC/S	Pharmaceutical Inspection Co-operation Scheme
QRM	Quality Risk Management
SAS	Special Access Scheme
TGA	Therapeutic Goods Administration