Comments on the

THERAPEUTIC GOODS ADMINISTRATION
CONSULTATION: ORPHAN DRUG PROGRAM

November 2016
1. WHAT IS NUCLEAR MEDICINE?

Nuclear medicine uses very small amounts of unsealed radioactive materials (radiopharmaceuticals) to diagnose a variety of different diseases. Nuclear medicine imaging is unique in that it provides information about both the anatomy of the body and its physiology (function).

In addition, nuclear medicine is also used therapeutically for the treatment of a range of conditions such as thyroid cancer, hyperthyroidism, lymphoma, neuroendocrine tumours, prostate cancer and bone pain caused by cancer metastasis.

Nuclear medicine imaging is used for diagnosis of a range of conditions including:

- Tumours
- Trauma
- Infections
- Irregular or inadequate blood flow to tissues
- Blood cell disorders and inadequate functioning of organs such as the thyroid gland and the lungs

Current nuclear medicine techniques include:

- Positron Emission Tomography (PET)
- Single Photon Emission Computed Tomography (SPECT) (cardiovascular imaging and bone scanning)
- Radionuclide Therapy

1.1 Positron Emission Tomography (PET)

PET and SPECT imaging are similar techniques in that they both utilise gamma rays given off by the radiopharmaceutical that is injected.

PET utilises short-lived radioactive isotopes; the PET camera detects the gamma rays given off at the site where a positron emitted from the radioactive substance collides with an electron in the tissue. Through a number of stages the PET camera enables the gamma rays to be converted to electrical signals that are processed by a computer to generate images; a series of many thin ‘slice’ images of the body can then be assembled into a three dimensional representation of the patient’s body.

PET provides images of blood flow or other biochemical functions. Increasingly PET is used in the detection and staging of cancers, particularly in metastatic spread, where glucose metabolism, resulting from the interaction of the radiopharmaceutical and the detection capability of PET cameras, enables metastases to be readily identified. The
results of PET scans significantly improve the ability of treating specialists to determine the best treatment options for each patient.

Through the use of PET scanning, the use of nuclear medicine for diagnosis of cancer and for identifying metastatic spread is increasing rapidly.

1.2 Single Photon Emission Computed Tomography (SPECT)

SPECT uses radioactive isotopes that are longer living than those for PET and emit single rather than double gamma rays. SPECT is a ‘mature’ technology in that is has been in use for many decades and is widely available to the Australian community.

A major cardiac SPECT imaging technique is the myocardial perfusion study, whereby the patient undergoes two studies, one with and one without exercise (or other stress); the before and after images enable changes in blood flow to the heart to be assessed, which is important in the evaluation of coronary artery disease.

1.3 Nuclear medicine as a specialty

In Australia, nuclear medicine services are provided by recognised specialists in nuclear medicine. Nuclear medicine is an advanced specialty in that the Advanced Training Program is undertaken either pre- or post-Fellowship of either the Royal Australasian College of Physicians (RACP) or the Royal Australian and New Zealand College of Radiologists (RANZCR).

There are currently approximately 420 credentialed specialists in nuclear medicine in Australia who deliver nuclear medicine services in approximately 200 sites across the country. The most common studies are bone scans, myocardial perfusion scans, lung and thyroid scans, which currently comprise 80 per cent of all studies. As a relatively new technology, PET scanning is growing rapidly, notwithstanding there is limited public funding of PET in Australia.

The AANMS is the main organisation in Australia representing the specialty of nuclear medicine. The AANMS takes a major role in the promotion and advancement of the clinical practice of nuclear medicine and is responsible for accreditation of both practices and training sites.

2. WHAT IS A RADIOPHARMACEUTICAL?

A radiopharmaceutical is a compound that nearly always consists of two or more components, namely the radionuclide itself (e.g. $^{99m}$Tc) and a molecule that determines the biodistribution and uptake within organs following administration. Using $^{99m}$Tc as an example, in this way $^{99m}$Tc can be bound to a bisphosphonate (e.g. methylene diphosphonate, MDP) to form $^{99m}$Tc-MDP, an agent commonly used for bone scanning.
Alternatively, $^{99m}\text{Tc}$ can be bound to a renal tubular agent (e.g. mercapto-acetyl glycine, MAG$_3$) to image the anatomy and function of the kidneys.

Rarely, the radionuclide in ionised form will constitute the entire radiopharmaceutical; e.g. sodium pertechnetate [$\text{NaTcO}_4$] is the product eluted from a Molybdenum-99 generator following immersion of the radioactive column in normal saline, and needs no further modification to perform a thyroid scan, or red blood cell labelling.

Sometimes the radionuclide cannot be bound directly to the carrier molecule and so a ligand is required to connect the two. In this way, $^{68}$Ga (a positron emitter, suitable for PET imaging) can be bound to DOTA (a common ligand used in peptide imaging), which in turn is bound to octreotate, an agent that targets somatostatin receptors, to form $^{68}$Ga-DOTA-octreotate (or $^{68}$Ga-DOTAtate).

The molecular tracers used in nuclear medicine may be purchased in kit or reconstituted form through Australian suppliers. Some products are not listed on the ARTG and may need to be imported from overseas under the Special Access Scheme (SAS). The latter scenario is becoming increasingly likely as the pace of scientific discovery exceeds the ability of industry or government regulators to respond, particularly in terms of evaluation of new products.

The short half-life of most radionuclides (most commonly six hours or less) means that the typical supply chain model relevant to other pharmaceuticals cannot be employed, and on-site (or near-site) reconstitution is required for immediate patient administration. There is effectively no shelf life for radiopharmaceuticals, an important distinction between radiopharmaceuticals and other diagnostic and therapeutic medicines.

Furthermore, with the exception of therapeutic radiopharmaceuticals, they are not drugs at all; rather, they are radiodiagnostic agents that do not have a therapeutic effect and, while they are generally used for common conditions, radiopharmaceuticals are not high volume because of Australia’s relatively small population.

3. SAFETY PROFILE OF RADIOPHARMACEUTICALS

Radiopharmaceuticals have an excellent safety profile, which has been established over decades among millions of patients. In a recently published series of more than one million radiopharmaceutical administrations from a group of hospitals in the United States, the incidence of any adverse events was estimated at approximately 1:100,000 administrations, and there were no life-threatening adverse reactions.¹ In Australia,

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where over 600,000 Nuclear Medicine studies are performed annually, reports of adverse events to regulatory agencies are exceedingly rare and the safety profile of radiopharmaceuticals in this country is well established.
COMMENTS ON CONSULTATION QUESTIONS

Proposed Orphan Designation Criteria:

1. Consultation Item 1 – Rare disease threshold, seriousness of the condition

The AANMS fully supports the criterion proposed in Consultation Item 1. The AANMS has noted previously that ‘rare’ diseases, and particular subtypes of more common diseases (i.e. those which require a particular molecular ‘signature’ to qualify for treatment) are collectively quite common in Australia. This change will benefit a significant number of patients who otherwise may not have access to valuable diagnostic tests because a relevant radiopharmaceutical may never otherwise be registered.

2. Consultation Item 2 – Existing treatment and significant benefit over existing treatment

The AANMS supports the criterion proposed in Consultation Item 2, with the proviso that the wording is changed to reflect the difficulties that would result for radiopharmaceuticals that are considered drugs for the purposes of registration, but are largely diagnostic agents and not therapies. This criterion is currently worded on the assumption that the drug for which registration is sought is a therapeutic, not a diagnostic, drug. As such, this criterion could inadvertently exclude all diagnostic agents, including radiopharmaceuticals, from consideration.

*The AANMS strongly recommends that the wording of this criterion be revised to ensure radiopharmaceuticals are not excluded under this criterion. The revised criterion should specifically include the words, “diagnostic agent” or “radiopharmaceutical”.*

3. Consultation Item 3 – Orphan condition, medical plausibility and biomarkers

The AANMS fully supports criteria three and four.

Other Consultation Items:

4. Consultation Item 4 – Paediatric populations

The AANMS supports the proposed consideration of paediatric indications.

5. Consultation Item 5 – Modifications to the designation process

The AANMS supports the proposed changes to the designation process and the timing of automatic lapsing.
6. Consultation Item 6 – Other considerations

6.1 Differences between radiopharmaceuticals and other pharmaceuticals.
As noted in Background Item 2 (p.4 above), and by the AANMS in its submission to the TGA’s Review of Orphan Drugs Program in 2015, there are significant differences between pharmaceuticals and radiopharmaceuticals. This includes the fact that radiopharmaceuticals do not represent significant sales in Australia, and the move towards increasing differentiation of target indication that is alluded to in the TGA’s Review paper does not routinely occur in nuclear medicine. However, as the criterion proposed at Consultation Item 2 has indicated, the differences between radiopharmaceuticals and pharmaceuticals appear to remain under-acknowledged. Although radiopharmaceutical manufacturers are not among the high users of the Orphan Drugs program, it is essential that these manufacturers have continued access to this program so that access to radiopharmaceuticals is maintained for Australian patients.

6.2 Reciprocity between regulators
The AANMS would reiterate the recommendation from its 2015 submission, that the TGA’s consideration of the Orphan Drugs program should also take into account other potential mechanisms for regulation in Australia, such as reciprocity. In order to bring down the cost and effort of regulatory approval in this country, the AANMS submits that it is possible to develop a list of “trusted” overseas regulatory bodies and that approval for marketing of any therapeutic good in that body’s jurisdiction should significantly reduce both the cost and time for a subsequent application for approval by the TGA in this country, or potentially even obviate the need for such approval altogether. This would provide an appropriate alternative to Orphan Drug registration in some cases.

The AANMS believes that reciprocal recognition has the ability to substantially improve availability of newer radiopharmaceuticals in this country without exposing the public to risk, particularly agents for which regulatory approval has been obtained in the United States or Europe, but which is not considered by the manufacturer to be commercially worthwhile in Australia. The AANMS again emphasises that in nuclear medicine, where minute quantities of pharmacological products are in use, the safety profile of diagnostic radiopharmaceuticals is very well established and any adverse events are exceedingly rare.

It is pleasing to see that the TGA is currently conducting a consultation on identification of comparable overseas regulators as providers of assessment reports and possible work-sharing partners in the assessment of medicine registration applications. The AANMS will submit in relation to the various TGA consultations that there must be clear
recognition of the differences between radiopharmaceuticals and pharmaceuticals and where relevant, that this is clearly stated in regulation.

6.3 Authorised Prescriber Scheme and Special Access Scheme

The AANMS believes that any consideration of the Orphan Drugs program should also include consideration of the two other schemes that allow access to products not currently registered in Australia. These are: Authorised Prescriber arrangements and the Special Access Scheme.

The Authorised Prescriber arrangements allow a medical practitioner to become an ‘Authorised Prescriber’ to individual patients in their immediate care without further TGA approval. These arrangements allow un-registered products to be used under particular conditions.

However, this process is also not without its complexities. The process of approval includes seeking endorsement from an Ethics Committee (either of the relevant hospital or, where the authorised prescriber is not a hospital employee, from a hospital located in ‘reasonable proximity’ to the individual).

Further, the current process for securing authorised prescriber endorsement is complex and can be very time consuming. While this may be practical in relation to products which are unlikely to ever achieve regulatory approval in this country, it is often the case in nuclear medicine that authorised prescriber status is requested because a product has not had its TGA approval renewed for commercial reasons, and as a result becomes ‘unapproved’.

It is understood that some changes to this process are under consideration by the TGA already (in relation to the organisations that may provide endorsement under the legislation) and the AANMS wishes to again urge the TGA to streamline these processes in order to make useful radiopharmaceuticals available to Australian patients.

Given the current problem of unavailability of certain radiopharmaceuticals in this country, the AANMS strongly endorses the continuation of the Special Access Scheme, through which these agents can be imported and notes that this is one of the mechanisms through which Australia patients may gain access to valuable radiopharmaceuticals that manufacturers have deemed uneconomic to register in Australia. Category A of the SAS currently allows importation of non-approved radiopharmaceuticals into this country for the management of patients with life-threatening conditions, while Category B is for other patients.

Any significant change to the Orphan Drugs program may affect the use of both the Authorised Prescriber arrangements and the Special Access Scheme.