AUSTRALASIAN ASSOCIATION of
Nuclear Medicine
Specialists (AANMS)

House of Representatives Standing Committee on Health, Aged Care and Sport Inquiry into the approval processes for new drugs and novel medical technologies in Australia

The Australasian Association of Nuclear Medicine Specialists (AANMS) and the Australian and New Zealand Society of Nuclear Medicine (ANZSNM) would like to thank the Standing Committee for initiating this inquiry and for the opportunity to make a submission.

The AANMS and ANZSNM are the peak bodies representing the clinical practice of nuclear medicine in Australia and New Zealand. The organisations work to advance nuclear medicine in practice, research and education.

AANMS and ANZSNM recognise that these issues, including those highlighted in this submission, are highly technical and complex. As subject matter experts in radiopharmaceuticals in Australia, AANMS and ANZSNM would welcome the opportunity to address the Committee in inquiry hearings to expand on the information provided in this submission and to assist in any way to further the objectives of the inquiry.

The submission from AANMS and ANZSNM addresses the Terms of Reference (TOR) for the inquiry.

1. **The range of new drugs and emerging novel medical technologies in development in Australia and globally, including areas of innovation where there is an interface between drugs and novel therapies.**
2. **Incentives to research, develop and commercialise new drugs and novel medical technologies for conditions where there is an unmet need, in particular orphan, personalised drugs and off-patent that could be repurposed and used to treat new conditions.**
3. **Measures that could make Australia a more attractive location for clinical trials for new drugs and novel medical technologies.**

This section will address the above TOR collectively.

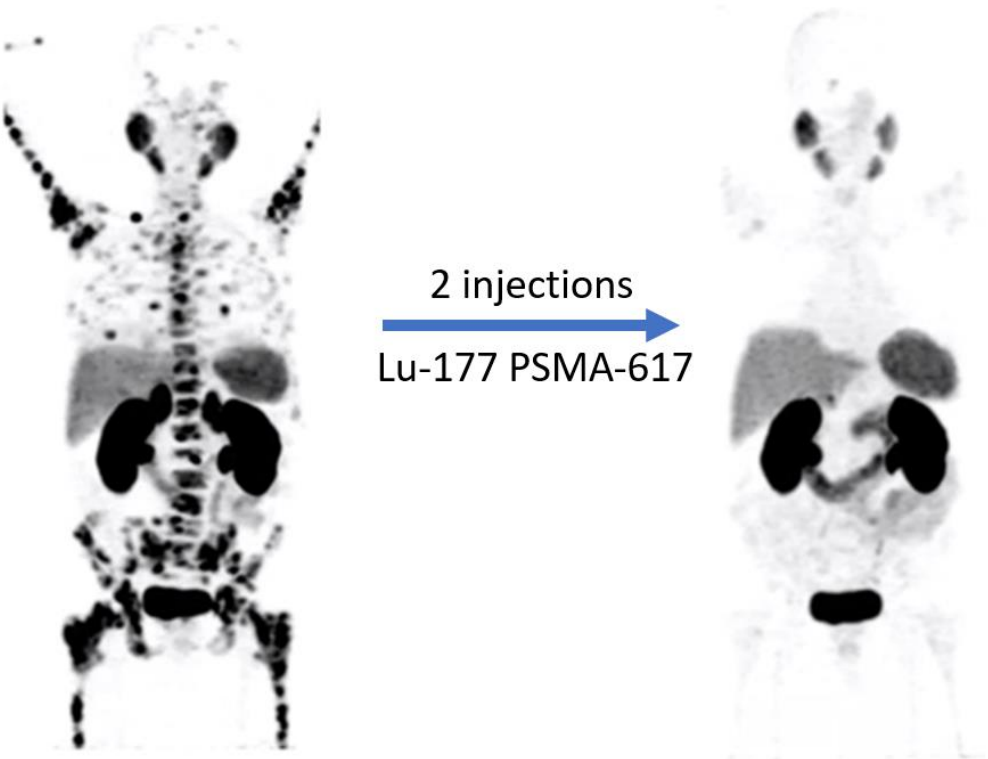
1. Background

Australia at this time has an opportunity to develop a new industry of national significance and has the foundations for a very strong competitive advantage compared to other countries in the development of novel radiopharmaceuticals and theranostics[1] in particular:

a) Because of the high impact on disease management, and cancer in particular, the utilisation of radiopharmaceuticals, including novel (unfunded) radiopharmaceuticals, is increasing dramatically in Australia. In particular, the number of positron emission tomography (PET) scanners in Australia, which are often involved in theranostic applications, has increased ten-fold in the last 15 years;
b) The relatively recent advances in theranostics are showing promise as major new cancer treatment strategies. Theranostic agents are radiopharmaceutical doublets which are used for both imaging and treatment. An imaging radioisotope is attached to a molecule that targets cancer cells, allowing imaging with a PET or single-photon emission computerised tomography (SPECT) scanner. Once the

[1] Theranostics is a term that has been developed to cover the use of a radiopharmaceutical for both diagnosis and, after demonstrating appropriate levels of concentration of the radiopharmaceutical in tumours, subsequent therapy.

cancer is shown to take up the radiopharmaceutical, the imaging radioisotope is substituted with a therapy radioisotope which delivers the radiation treatment directly to the cancer cells via a single intravenous injection, with minimal radiation to non-malignant cells. This strategy is proving to be a highly effective therapy for prostate cancer and neuro-endocrine tumours. The figure below shows an example of a patient with very extensive prostate cancer before and after such treatment. The images are PET scans and show near-complete resolution of the cancer. These treatments are very well tolerated compared with conventional cancer treatments such as chemotherapy or external beam radiotherapy[2];



c) The therapy radioisotope most commonly used currently is lutetium-177 (Lu-177) [3] which is manufactured by the Australian Nuclear Science and Technology Organisation (ANSTO) at Lucas Heights in Australia. There are limited production facilities worldwide which manufacture Lu-177;
d) The radiation emitted by Lu-177 includes a beta particle. This type of radiation has a range in the body which spans about 30 cancer cells. A potentially more favourable class of therapeutic radionuclides are alpha emitters. Alpha radiation kills cancers with a range of around 3 cells and is much more potent than beta emissions; and
e) The science of clinical radiochemistry has advanced rapidly in recent years. Researchers around the world are developing novel radiopharmaceuticals for use as theranostic agents against a wide range of cancers including those which currently have very poor survival, such as ovarian, brain and pancreatic cancers.

[2] Image provided by Prof Michael Hofman, Peter Macallum Cancer Institute
[3] Lutetium (Lu-177) is the radionuclide used most frequently at present in targeted radionuclide therapy (TRT)

2. Australia's strategic advantage

Australia is extraordinarily well positioned to take a world leadership position in development, production and clinical trials of radiopharmaceuticals and theranostics for the following reasons:

a. ANSTO has the Open Pool Australian Lightwater (OPAL) reactor at Lucas Heights and associated processing facilities for the production of medical radioisotopes, some of which are in very short supply worldwide;
b. Australia has large amounts of the precursor elements to produce the desirable alpha emitters for theranostics. Some of these are available at high concentrations in existing mining waste stockpiles;
c. Australia has world-leading expertise in materials processing, including of radioactive materials. The Commonwealth Scientific and Industrial Research Organisation (CSIRO) and ANSTO have particular expertise in this area;
d. The Australian Radioactive Waste Agency (ARWA) should be available in the future to manage the radioactive waste generated by the industry;
e. Australia has invested heavily in the National Imaging Facility (NIF) which provides radiochemistry for animal and human imaging capabilities to allow the testing of novel radiopharmaceuticals prior to their use in humans;
f. CSIRO and ANSTO have expertise in many key related areas:
    i. Radioactive bulk materials handling
    ii. Bioinformatics to identify suitable cancer targets
    iii. A peptide phage library to identify suitable molecules to target on the cancer cells
    iv. Radiochemistry capability to label candidate molecules for laboratory and animal testing prior to first in human studies
g. The Australian Nuclear Medicine community is recognised as a global leader in undertaking radiopharmaceutical theranostics trials. This has been leveraged off the following national capabilities:
    i. Australia has a high-quality health system with a highly developed, advanced nuclear medicine capability
    ii. Australia has numerous academic and hospital-based radiopharmacies, as well as commercial radiopharmacies, capable of manufacturing novel radiopharmaceuticals
    iii. A growing body of Australian intellectual capacity and research and leadership that is world leading in Alzheimer's, Prostate and other diseases
h. Australia is a comparatively inexpensive location to undertake radiopharmaceutical clinical trials;
i. The Australian Radiopharmaceutical Trials Network (ARTnet) is the envy of the rest of the world. This is a cooperative trials group of Nuclear Medicine experts and an Australia-wide network of nuclear medicine facilities focused on radiopharmaceutical clinical trials. ARTnet facilitates rapid commencement and completion of clinical trials and sets the national standards for accreditation of radiopharmaceutical production for clinical trials. It also undertakes a national certification of PET & SPECT scanners for participation in clinical trials; and
j. Australia has a very favourable regulatory environment for performance of radiopharmaceutical clinical trials, with the Therapeutic Goods Administration (TGA) Clinical Trials Notification (CTN) pathway.

3. The opportunity

Australia's strategic advantages and existing infrastructure creates a global opportunity. With relatively limited but targeted investment and with national coordination, Australia could become a world leader in the introduction of radiopharmaceuticals in general and theranostics in particular. This could become a significant national industry generating economic returns, employment and expertise. It would also give Australian patients early access to the latest treatments in trials and novel therapies. Such an industry would involve radiopharmaceutical discovery, development, clinical trials and ultimately clinical drug manufacture

or IP licencing. This industry would leverage on prior and planned government investment in the OPAL nuclear reactor, CSIRO, NIF and ARWA, alongside the expertise and "human capital" we possess.

Theranostics is a rapidly advancing field with potential for substantial economic benefit to the country and for health benefits to patients. As an example of the scale, Novartis recently paid approximately US$6 billion to acquire just two theranostic molecules (Ga-68/Lu-177 PSMA and Ga-68/Lu-177 DOTATATE).

Not only could Australia become a supplier of radiopharmaceuticals/theranostics to the world but it would establish its own internal, secure supply chain which would reduce the impact of the disruption to global supply chains which has affected patient care during the COVID pandemic.

4. Recommendations

AANMS and ANZSNM recommend:

1. The government targets the radiopharmaceutical industry for special assistance to develop a nationally significant industry.
2. The government ensure national unification of strategic intent and coordination of investment in the existing, largely government funded, assets such as CSIRO, ANSTO and NIF towards the development of a national scale radiopharmaceutical industry.
3. The government prioritise research funding from the Medical Research Future Fund (MRFF), NHMRC and other funding and research support agencies towards radiopharmaceutical drug discovery and clinical translation.
4. The government provide industry support and funding to ensure that intellectual property, drug discovery and manufacture are retained in Australia.

4. Without compromising the assessment of safety, quality, efficacy or cost-effectiveness, whether the approval process for new drugs and novel medical technologies, could be made more efficient, including through greater use of international approval processes, greater alignment of registration and reimbursement processes or post market assessment.

This section will address the above TOR number 4.

Consideration should be given to a new “class” of “drug” that is a “radiopharmaceutical”. Radiopharmaceuticals require special consideration as they have a substantially different context to conventional drugs submitted for approval of manufacture (*Therapeutic Goods Act* Part 3-3-manufacturing of therapeutic goods) and submitted for registration and listing on the Australian Registry of Therapeutic Goods (*Therapeutic Goods Act* Part 3-2):

a. Radiopharmaceuticals are largely diagnostic agents, not therapeutic agents.
b. They are generally single use.
c. The mass of the “pharmaceutical” administered is sub-pharmacologic (typically in nanomolar concentrations) and therefore radiopharmaceuticals usually do not have any physiological or pharmacological effect on the body.
d. The safety profile of radiopharmaceuticals is extremely favourable (for example, the incidence of *any* side effects from F18-FDG[4], the most commonly used PET radiopharmaceutical, is less than 1 in

[4] Fluorodeoxyglucose F18 Injection (FDG) is a positron emitting radiopharmaceutical used for diagnostic, staging and monitoring purposes in conjunction with PET

100,000). In comparison, the incidence of reactions or adverse events from radiological contrast is of the order of 1-3%.

e. Radiopharmaceuticals are not currently subsidised through the Pharmaceutical Benefits Scheme (PBS), but rather their cost is incorporated into the reimbursement of the nuclear medicine procedure, in those instances where the procedure is funded as an item in the Medicare Benefits Schedule (MBS). There is no current funding mechanism for radiopharmaceutical "drugs" other than the MBS.

f. Because radiopharmaceuticals are single use diagnostic agents and Australia is an inconsequential market in global terms, it is frequently uneconomic for a sponsor to apply for their product to be listed on the Australian Register of Therapeutic Goods (ART. Most new radiopharmaceuticals entering clinical use in Australia therefore bypass the ARTG and are used under various exemptions of the *Therapeutic Goods Act* (most commonly via the extemporaneous manufacturing provisions or the Special Access Scheme).

g. Radiopharmaceuticals are usually not manufactured centrally in large facilities for global/national distribution. This is not possible due to the short half-lives of the radionuclides which form part of the radiopharmaceutical. (For example, the half- life of fluorine-18, the most commonly used PET tracer, is 110 minutes). This mandates that the vast majority of radiopharmaceuticals are manufactured "just in time" (usually same day) and close to the point of use to minimise transport delays. For example, FDG is manufactured each day in approximately 15 facilities around Australia using various different production methodologies. This production scenario does not fit with the existing legislation and practice governing "drug" registration and listing on the ARTG.

h. In spite of the inherently low risk of radiopharmaceuticals, there is no distinction between the GMP production requirements for radiopharmaceuticals and conventional drugs under the *Therapeutic Goods Act* (Part 3-3- manufacturing of therapeutic goods). This creates a high barrier to the production of radiopharmaceuticals under TGA oversight in Australia. Due to the decentralised nature of radiopharmaceutical production, there are many production facilities producing and distributing radiopharmaceuticals that do not have the resources to achieve a GMP licence to manufacture, and they do so under exemption from the *Therapeutic Goods Act*:

    i. MBS rebates for nuclear medicine procedures are normally contingent on any radiopharmaceuticals used for the procedure to be listed on the ARTG. As it is generally not financially viable for a drug sponsor to apply for listing, Medical Services Advisory Committee (MSAC) applications for new nuclear medicine procedures are problematic. This restricts the access of Australian patients to new advances in nuclear medicine imaging (*e.g.* [I-123] DATscan® (GE Healthcare) for the diagnosis of Parkinson's Disease has been available in the USA & Europe for over 20 years but is still not available in Australia).

j. Patient access to nuclear medicine procedures is limited by the existing manufacturing framework. Radiopharmaceuticals manufactured under exemption:

    I) are not able to be shipped interstate and not able to be shipped within the same state from public facilities to private facilities due to TGA restrictions. For example, because the FDOPA[5] PET tracer is only produced in hospital radiopharmacies in three states, babies from other states with congenital hyperinsulinism have to fly interstate to have their FDOPA PET scan. These babies are very unwell and must fly with a medical support team. Instead of flying the baby to the PET tracer, ideally the PET tracer should be flown to the baby which would be both safer for the patient and of lower cost.; and

    II) There is lack of clarity about who are "exempt persons" able to manufacture radiopharmaceuticals under "exemption" as defined in the Therapeutic Goods

[5] Fluorodopa (FDOPA) is indicated for use in PET.

Regulations. Further, expansion of the classes of exempt persons should be considered to improve patient access to nuclear medicine procedures.

Recommendations:

AANMS and ANZSNM recommends:

1. Radiopharmaceuticals be considered as a separate class of "drug" for the purposes of assessment for registration on the ARTG.
2. The assessment of diagnostic radiopharmaceuticals for registration and listing on the ARTG requires a level of evidence commensurate with the markedly reduced risk of these radiopharmaceuticals.
3. The application costs for radiopharmaceuticals is reduced commensurate with the level of evidence required for assessment, and in recognition of the lack of commercial sponsors for these products, in order to reduce the barriers to registration which currently push radiopharmaceuticals down the pathways of exemptions from listing on the ARTG.
4. The manufacturing requirements for radiopharmaceuticals under the *Therapeutic Goods Act* be commensurate with the low risk of these procedures. Other jurisdictions have adopted a "GMP light" approach to radiopharmaceutical production.
5. The existing use of Comparative Overseas Regulators should be extended and with regard to radiopharmaceuticals, commensurate with the relatively low risk categorisation of these agents. There are many radiopharmaceuticals registered in overseas jurisdictions that are not registered in Australia. For example, there are three amyloid PET tracers approved in the USA for the diagnosis of Alzheimer's disease. There are no such agents approved in Australia we suspect due to regulatory hurdles and cost compared to commercial returns. In particular, radiopharmaceuticals with long approval histories and proven safety profiles should have low barriers for adoption of approval in Australia.
6. The current restriction on inter- and intra-state supply of radiopharmaceuticals manufactured under TGA exemption be reviewed in light of their favourable safety profile. In particular, the restriction on interstate supply of novel radiopharmaceuticals needs to be examined. Similarly, the supply of novel radiopharmaceuticals unable to be supplied by commercial radiopharmacies should be possible between public and private facilities manufacturing under exemption to other public and private facilities.
7. The difficulty and expense of change of sponsor of an existing listed drug should be minimised. In recent years, existing listed drugs have dropped off the ARTG when a new sponsor elects not to seek change of registration. This results in nuclear medicine practices having to use the SAS pathway to use a proven drug which was once, but is no longer, on the ARTG.