Draft framework for the MSAC assessment of radiopharmaceuticals

Radiopharmaceuticals are unique in their mechanism of action (radioactivity rather than pharmacological), supply chain requirements and operational management characteristics compared with other types of medicines**.** The purpose of this Framework is to identify the supplementary information requirements to those set out in the Guidelines for preparing assessments for the Medical Services Advisory Committee ("MSAC Guidelines") to ensure that radiopharmaceuticals to be used within the scope of a proposed MBS item descriptor in an application for a new or amended MBS item are adequately characterised and produced according to accepted standards, in order to be evaluated for clinical (diagnostic or therapeutic) noninferiority against a comparator product[1] or products. The question of noninferiority of radiopharmaceuticals has arisen in the context of several MSAC applications. For example, there may be a scarcity or lack of evidence to inform the safety and efficacy of a radiopharmaceutical product or products for which a new or amended MBS item descriptor(s) is being proposed, and the applicant may cite evidence for the comparator(s) as the best available evidence on which to base a claim of clinical noninferiority between the two products.

With the exception of radionuclide generators, this Framework includes all radiopharmaceuticals which are:

(i) for diagnostic imaging or
(ii) for nuclear medicine therapy; and
(iii) within the scope of a proposed MBS item descriptor **in an application for a new or amended MBS item.**

The above includes radiopharmaceuticals which are:

(i) Therapeutic Goods Administration (TGA)-approved with Good Manufacturing Practice (GMP), as identified by being included on the Australian Register of Therapeutic Goods (ARTG)
(ii) TGA unapproved or exempt from inclusion on the ARTG
(iii) Special Access Scheme (SAS)/Authorised Prescriber supplied.

This Framework and MSAC assessment applies for the purpose of MBS listing only. Applicants must satisfy themselves in relation to the requirements of the *Therapeutic Goods Act 1989* and other applicable legislation.

[1] Note: The comparator product may or may not be the comparator within the health technology assessment, but will be the comparator from which the evidence base was derived.

Aspects to be considered when assessing whether radiopharmaceuticals within the scope of a proposed MBS item descriptor are noninferior to a similar product

1. Preclinical aspects

1A. Radiopharmaceuticals listed on the Australian Register of Therapeutic Goods (ARTG)

Applications for a new or amended MBS item for radiopharmaceuticals already included on the ARTG are not required to provide additional information as listed below (1B) or in Attachment A regarding production and quality control as such radiopharmaceuticals are considered to be well-characterised by the TGA Australian Product Information document, and produced to a satisfactory quality standard by virtue of having been produced under Good Manufacturing Practice (GMP) rules and having undergone an assessment of quality and technical safety by the TGA.

1B. Therapeutic Goods Administration (TGA) unapproved or exempt radiopharmaceuticals

This Framework and MSAC assessment applies for the purpose of MBS listing only. Applicants must satisfy themselves in relation to the regulatory requirements of the TGA in relation to unapproved or exempt therapeutic goods not included on the ARTG. Supply of the following information to MSAC is not a substitute for meeting TGA information requirements.

Applications for a new or amended MBS item that includes the use of a TGA unapproved or exempt radiopharmaceutical(s) (including SAS/Authorised Prescriber supplied) are required to provide information on the following characteristics of the new radiopharmaceutical product(s) proposed for listing:

- Product name.
- Composition:
  - chemical structure;
  - physical characteristics, including decay chart & radiation emissions;
  - external radiation & shielding requirements;
  - radiation dosimetry – including effective dose & critical organ(s).
- Pharmaceutical form:
  - preparation & administration;
  - vehicle & excipients;
  - incompatibilities;
  - shelf life.
- Pharmacology:
  - mechanism of action;
  - pharmacokinetics:
    - biodistribution;
    - metabolism & excretion.
- Safety:
  - contraindications;

- precautions, including:
  - extravasation risks;
  - radiation risks – including use in pregnancy / lactation / paediatrics;
  - use in organ (e.g., renal / liver / bone marrow) impairment;
  - medicine interactions;
- adverse effects.

To facilitate the evaluation, the applicant should tabulate information corresponding to each of the above product characteristics for the radiopharmaceutical proposed for listing against corresponding information for the comparator product.

Applicants are also required to provide supplementary information as detailed in **Attachment A** regarding the production and quality control of the proposed radiopharmaceutical(s).

This information will be used to determine if the preclinical aspects (composition, pharmacokinetics, dosimetry, etc) of the proposed radiopharmaceutical have been sufficiently well-characterised and that the proposed radiopharmaceutical is produced to a satisfactory quality standard. Once these elements have been established, the assessment of a claim of clinical noninferiority of the proposed product against the comparator product (for diagnostic radiopharmaceuticals: comparative test accuracy; and for therapeutic radiopharmaceuticals: comparative extent of therapeutic effect) can then proceed according to the MSAC Guidelines.

2. Clinical aspects

The relevant sections of the MSAC Guidelines for the assessment of a clinical claim of noninferiority of the proposed radiopharmaceutical against the comparator product are as follows:

- *MSAC Technical Guidance (TG) 11: Linked evidence – test accuracy for "comparative test accuracy"* for **diagnostic radiopharmaceuticals** and
- *MSAC TG 6: Effectiveness of therapeutic technologies and TG 7: Safety of therapeutic technologies for "comparative extent of therapeutic effect (both safety and effectiveness)"* for **therapeutic radiopharmaceuticals**.

ATTACHMENT A: RADIOPHARMACEUTICAL APPLICATION CHECKLIST FOR RADIOPHARMACEUTICALS *NOT REGISTERED* ON THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (ARTG)

A) Is the proposed RP produced under a current Therapeutic Goods Administration (TGA) manufacturing licence?

☐ YES: *Please provide TGA licence details.*

☐ NO: *Please complete Sections B & C.*

B) Standard Requirements:

1. There is a Standard Operating Procedure (SOP) for material management, including control and checks on all raw materials (chemicals or gas).

☐ YES: *Please provide a copy of the procedure sample or equivalent guiding document.*

☐ NO: *Please justify.*

2. The batch master file specifies a label that includes pharmacopoeia name, activity, reference and expiry time, instructions for storage, and precautions. Copies of labels are retained and the total number of labels is reconciled before final quality control (QC) release of batch.

☐ YES.

☐ NO: *Please justify.*

3. There are SOPs for the various steps of the production process, based on best practice or relevant literature methods.

☐ YES: *Please provide a copy of the procedure sample or equivalent guiding document.*

☐ NO: *Please justify.*

4. There are SOPs for QC methodology and testing, based on pharmacopeia or equivalent validated methods.

☐ YES: *Please provide a copy of the procedure sample or equivalent guiding document.*

☐ NO: *Please justify.*

5. There is routine microbiological monitoring of the preparation area and the aseptic dispensing station in the radiopharmacy. The quality controller independently performs all required microbiological assessments, filter integrity tests, endotoxin tests, plates controls, end of broth, contact plates, sterility testing, other (specify).

☐ YES.

☐ NO: *Please justify.*

6. There is a tested product recall procedure to ensure radiopharmaceuticals are not administered to patients before receipt of the product release document.

☐ YES: *Please provide a copy of the procedure sample or equivalent guiding document.*

☐ NO: *Please justify.*

7. There is a timely transmission of a product release document/certificate of analysis to end users and follow-up of deficiencies, complaints and feedback.

☐ YES: *Please provide a copy of the procedure sample or equivalent guiding document.*

☐ NO: *Please justify.*

8. There is an SOP for packing and safe transportation requirements in accordance with ARPANSA guidelines[2].

☐ YES: *Please provide a copy of the procedure sample or equivalent guiding document.*

☐ NO: *Please justify.*

9. There are jurisdictional-compliant radioactive[3] and hazardous[4] waste disposal practices.

☐ YES.

☐ NO: *Please justify.*

[2] Radiation Protection Series C-2 (Rev. 1) | ARPANSA
[3] State & territory regulators | ARPANSA
[4] State and territory hazardous waste requirements - DCCEEW

C) Required Quality Control Criteria:

Characteristic	**Specification** (if *not* tested, please provide justification)	**Methodology** (include reference standard, e.g. EP, USP, ICH)
Appearance		
pH		
Chemical purity		
Impurities		
Molar activity		
Radionuclidic purity		
Radiochemical purity		
Radioactive concentration		
Sterility		
Endotoxin testing		

EP: European Pharmacopoeia; ICH: International Council for Harmonisation; USP: United States Pharmacopeia