Health Canada Santé Canada

Radiopharmaceuticals, Kits, and Generators: Submission Information for Schedule C Drugs

Guidance document

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Canada

Health Canada is the federal department responsible for helping the people of Canada maintain and improve their health.

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Radiopharmaceutiques, trousses et générateurs : Renseignements pour les présentations de médicaments de l'annexe C
Ligne directrice

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Foreword

Guidance documents are meant to provide assistance to industry and health care professionals on **how** to comply with governing statutes and regulations. Guidance documents also provide assistance to staff on how Health Canada mandates and objectives should be implemented in a manner that is fair, consistent, and effective.

Guidance documents are administrative instruments not having force of law and, as such, allow for flexibility in approach. Alternate approaches to the principles and practices described in this document ***may be*** acceptable provided they are supported by adequate justification. Alternate approaches should be discussed in advance with the relevant programme area to avoid the possible finding that applicable statutory or regulatory requirements have not been met.

As a corollary to the above, it is equally important to note that Health Canada reserves the right to request information or material, or define conditions not specifically described in this document, in order to allow the Department to adequately assess the safety, efficacy, and quality of a drug. Health Canada is committed to ensuring that such requests are justifiable and that decisions are clearly documented.

This document should be read in conjunction with the accompanying notice and the relevant sections of other applicable Guidance documents.

Table of Contents

See Section 2 - How to use this document for a description of how to jump forwards and backwards from this Table of Contents.

1. INTRODUCTION

Schedule C drugs are radiopharmaceuticals, kits, and generators.

They are listed on Schedule C to the *Food and Drugs Act* as radiopharmaceuticals (including radionuclide generators), and drugs other than radionuclides (kits and components of kits) for use in the preparation of radiopharmaceuticals.

Health Canada is the national regulatory authority that evaluates the safety, efficacy, and quality of drugs, including Schedule C drugs, for authorization to sell them in Canada.

1.1. OBJECTIVE

The objective of this Guidance document is to set out Health Canada's Schedule C-specific submission data expectations for Clinical Trial Applications (CTA), New Drug Submissions (NDS), and Abbreviated New Drug Submissions (ANDS). The document helps sponsors satisfy requirements under Canada's *Food and Drugs Act* and Regulations.

The 2 key starting sections to read are Section 1.2 - Scope, and Section 2 - How to use this document.

1.2. SCOPE

This Guidance document applies to all drugs set out in Schedule C to the *Food and Drugs Act* of chemical or biological origin with the following exceptions:

- Section 5 of this Guidance document: the ANDS pathway does not apply to Schedule C drugs containing biological entities; and
- Positron Emitting Radiopharmaceuticals (PERs) used in basic clinical research studies: this Guidance does not apply as there is a separate Guidance to use instead – see Section 6.1.3 - Basic research in this document for its reference.

A note for Sections 3-5 of this Guidance document: All requested Non-clinical and Clinical submission data apply to both diagnostic and therapeutic Schedule C drugs unless otherwise stated, as diagnostics and therapeutics do not present many differences with respect to submission data. Therapeutic Schedule C drugs generally follow what is recommended for other therapeutic drugs.

The following principles guide the request for submission data outlined in this document:

- Schedule C drugs are different from other drugs because of their unique properties of radioactivity for which this Guidance document sets out Schedule C-specific submission data (Sections 3-7 in this document).
- Schedule C drugs are like other drugs in that they are subject to the same general submission requirements and same processes for obtaining market authorization in Canada as other drugs (Section 6 in this document).

The content of this document does not intend to cover every conceivable case. Alternate means of complying with the data information outlined can be considered with appropriate scientific justification. Different approaches may be considered as new

technologies emerge. International guidance, like that of the EMA or FDA, may be used to provide a rationale if Health Canada does not provide specific guidance.

Note:

- In this document, "sponsor" refers to:
  - the individual, corporate body, institution or organization that is responsible to Health Canada for a clinical trial;
  - the manufacturer (DIN or NOC owner) of a marketed drug product.

- In this document, "shall" is used to express a requirement, i.e., a provision that the user is obliged to satisfy in order to comply with the regulatory requirements; "should" is used to express a recommendation which is advised but not required; and "may" and “can” are used to express an option which is permissible within the limits of the Guidance document.

- In the French version of this document, terms like “drogue” and “présentation de drogue nouvelle” are used in order to match terminology in the *Food and Drugs Act* and Regulations; otherwise, the equivalent and more prevalent term “médicament” is used. Likewise, the term “produit pharmaceutique radioactif” is used when referring to the *Food and Drugs Act* and Regulations; otherwise the equivalent term “radiopharmaceutique” is used in the French version of this document as a noun for terms like “REG (radiopharmaceutique émetteur de gamma)”, “REP (radiopharmaceutique émetteur de positrons”), or “NGNP (radiopharmaceutique qui n’émet ni gamma ni positrons)”.

- In this document, references including in Appendix A, are deliberately not linked to URLs. Sponsors should search on the web for these documents using the documents’ titles.
  - The reality of Government of Canada websites is that URLs change frequently and without warning. This instantly voids the relevance of the link and would result in this Guidance document being quickly and unnecessarily out-of-date. To mitigate this, the Guidance lists titles of documents, without URLs, so that the user can web search for the relevant words in the title, which are less likely to change through time. In this way, this Guidance document will remain up-to-date for longer.

2. HOW TO USE THIS DOCUMENT

The following is an explanation for a general PDF feature to use in this Guidance document.

There is a functionality of jumping forwards and backwards within this document:

- to jump forwards to a chosen section, place the cursor over the line in the Table of Contents or over the section number in the body of the text, then click;

then

- to immediately jump back, press ALT and left arrow.

This functionality is available:

- in 4 separate Tables of Contents, where the first is at the start of the Guidance for the whole document, and the others are at the start of each stand-alone CTA, NDS, and ANDS section;
- in Table 1 directly below, which provides shortcuts to jump within the CTA, NDS, and ANDS sections;

and

- in references throughout the body of the text e.g., "see Section 6.1. – Key Health Canada Guidances."

This Guidance document is to be used as a reference tool as per Table 1[1] below, where sponsors can refer to their needed sections, and do not need to read the whole document from beginning to end.

For example, a sponsor submitting an NDS for a Schedule C drug that is a diagnostic GER should submit the information outlined in Section 4.1.1. (Quality - GERs), in Section 4.2. (Non-clinical - diagnostics or therapeutics), and in Section 4.3. (Clinical - diagnostics or therapeutics.

TABLE 1: Grid structure with shortcuts to jump to submission data in the CTA, NDS, and ANDS sections

Data	CTA	Section	NDS	Section	ANDS	Section
Quality	GERs	3.1.1	GERs	4.1.1	GERs	5.1.1
	PERs	3.1.2	PERs	4.1.2	PERs	5.1.2
	NGNP	3.1.3	NGNP	4.1.3	NGNP	5.1.3
	Generators	3.1.4	Generators	4.1.4	Generators	5.1.4
	Kits	3.1.5	Kits	4.1.5	Kits	5.1.5
Non-clinical	Diagnostics or Therapeutics	3.2	Diagnostics or Therapeutics	4.2	Diagnostics or Therapeutics	5.2

[1] CTA = Clinical Trial Application, NDS = New Drug Submission, ANDS = Abbreviated New Drug Submission, GER = Gamma Emitting Radiopharmaceutical, PER = Positron Emitting Radiopharmaceutical. For the full listing of all acronyms used in the document, see Section 2.2 - Acronyms.

Data	CTA	Section	NDS	Section	ANDS	Section
Clinical	Diagnostics or Therapeutics	3.3	Diagnostics or Therapeutics	4.3	Diagnostics or Therapeutics	5.3

2.1. FEATURES TO HELP THE USER

- The CTA, NDS, and ANDS sections (Sections 3-5) are the core of this Guidance document. They are stand-alone, because the most likely way sponsors will use the document is to submit a CTA or NDS or ANDS at distinct points in time. The 3 sections are tied together at the front end of the document with a short introduction (Sections 1-2) and in the back end of the document with 2 appendices (Sections 6-7).
- Submission data for the CTA, NDS, and ANDS sections are structured as a grid (see Table 1 above), with equivalent numbering "horizontally" from CTA to NDS to ANDS, that is predictable and consistent in order to help the user navigate a long document with a high degree of repeated text.
    - For example, Sections 3.1.2, 4.1.2, and 5.1.2 are about Quality information for PERS in CTAs, NDS, and ANDS respectively; and Sections 3.3.1.1, 4.3.1.1, and 5.3.1.1 are for Clinical information for Primary Pharmacodynamics in CTAs, NDS, and ANDS sections respectively.
- There are some sections in the Guidance, like Section 5.3.1.1, that do not list submission data and instead state "This section exists for CTA and NDS only, and is not applicable to ANDS." These sections function as placeholders in order to maintain the numbering sequencing of the CTA-NDS-ANDS grid structure in Table 1, to give a general sense of comparison of what is the same and different amongst CTA-NDS-ANDS data expectations.

For a quick overview of submission data from CTA to NDS to ANDS, see Section 7 - APPENDIX B – Overview comparison of CTA-NDS-ANDS. The 3 tables in Appendix B compare which Quality, Non-Clinical, and Clinical submission data apply to CTA, NDS, and ANDS.

- In general, there are more submission data that are the same than different amongst CTA-NDS-ANDS, which means that there is a high degree of repetition in the Guidance. The document is hence structured in multiple ways to help the user know in which section they are located:
    - The header in the right top margin, and the footer in the right bottom margin indicate the ***section*** of the Guidance document i.e., CTA, NDS, or ANDS.
    - The footer in the right bottom margin indicates ***both*** page numbers for that particular section and page numbers for the Guidance as a whole, as the Guidance is designed for its CTA, NDS, ANDS sections to be stand-alone.
    - In addition to the Table of Contents for the Guidance as a whole, the beginning of each of the CTA, NDS, and ANDS sections has a ***sub-Table of Contents*** for that section.

- Finally, the document distinguishes between what submission data the sponsor should provide to Health Canada vs what is an accompanying explanation to help with the requested submission data. The former is written in the format of "the sponsor should provide ...." where submission data is listed in a bulleted, checklist kind of way; the latter is written differently e.g., see "note".

2.2. ACRONYMS

Please refer to the following list for the acronyms used in this document. Full terms are not used from this point forward, as this document is to be used as a reference tool where the user moves forwards and backwards throughout the document.

- ANDS = Abbreviated New Drug Submission *(PADN = Présentation abrégée de drogue nouvelle)*
- API = Active Pharmaceutical Ingredient *(IPA = Ingrédient pharmaceutique actif)*
- BGTD = Biologics and Genetic Therapies Directorate *(DPBTG = Direction des produits biologiques et des thérapies génétiques)*
- C of A = Certificate of Analysis *(CA = Certificat d'analyse)*
- CNSC = Canadian Nuclear Safety Commission *(CCSN = Commission canadienne de sûreté nucléaire)*
- CRP = Canadian Reference Product *(PRC = Produit de référence canadien*)
- CT = Computed Tomography *(TDM = Tomodensitométrie)*
- CTA = Clinical Trial Application *(DEC = Demande d'essai clinique)*
- CTD = Common Technical Document
- DEL = Drug Establishment License *(LEPP = Licence d'établissement de produits pharmaceutiques)*
- DIN = Drug Identification Number *(DIN = Identification numérique de drogue)*
- DMF = Drug Master File *(FMM = Fiche maîtresse de médicaments)*
- GER = Gamma-emitting Radiopharmaceutical *(REG = Radiopharmaceutique émetteur de gamma)*
- GCP = Good Clinical Practices *(BPC = Bonnes pratiques cliniques)*
- GLP = Good Laboratory Practices *(BPL = Bonnes pratiques de laboratoire)*
- GMP = Good Manufacturing Practices *(BPF = Bonnes pratiques de fabrication)*
- IB = Investigator's Brochure *(BC = Brochure du chercheur)*
- ICH = International Conference on Harmonisation
- ICRP = International Commission on Radiological Protection *(CIPR = Commission internationale de protection radiologique)*
- MHPD = Marketed Health Products Directorate *(DPSC = Direction des produits de santé commercialisés)*
- MIRD = Committee on Medical Internal Radiation Dose *(MIRD = Schéma de la dose de rayonnement interne médical)*
- NDS = New Drug Submission *(PDN = Présentation de drogue nouvelle)*
- NGNP = Non-GERs Non-PERs Radiopharmaceutical *(NGNP = Radiopharmaceutique qui n'émet ni gamma ni positrons)*
- NOAEL = No Observed Adverse Effect Level *(DSENO = Dose sans effet nocif observé)*
- NOC = Notice of Compliance *(AC = Avis de conformité)*

- PBRER = Periodic Benefit-Risk Evaluation Report *(RPEAR = Rapport périodique d'évaluation des avantages et des risques)*
- PER = Positron-emitting Radiopharmaceutical *(REP = Radiopharmaceutique émetteur de positrons)*
- PET = Positron Emission Tomography *(TEP = Tomographie par émission de positrons)*
- PM = Product Monograph *(MP = Monographie de produit)*
- PSUR = Periodic Safety Update Report *(RPPV = Rapport périodique de pharmacovigilance)*
- QT = Q wave and T wave *(QT = onde Q et onde T)*
- RMP = Risk Management Plan *(PGR = Plan de gestion des risques)*
- ROEB = Regulatory Operations and Enforcement Branch *(DGORAL = Direction générale des opérations réglementaires et de l'application de la loi)*
- SAP = Statistical Analysis Plan *(PAS = Plan d'analyse statistique)*
- SOP = Standard Operating Procedure *(PON = Procédure opérationnelle normalisée)*
- SPECT = Single-photon Emission Computed Tomography *(TEM = Tomographie d'émission monophotonique)*
- USP = United States Pharmacopeia

3. SECTION CTA – SUBMISSION DATA SPECIFIC TO SCHEDULE C DRUGS FOR CLINICAL TRIAL APPLICATIONS

See Section 2 - How to use this document for a description of how to jump forwards and backwards from the sub-Table of Contents for the CTA section.

The overview of SECTION CTA is:

Note: An IB should be submitted with the CTA. The IB should provide quality, non-clinical, and clinical information to the investigator. The IB should contain information set out in Section 6.1 – Key Health Canada Guidances.

3.1. QUALITY SUBMISSION DATA

Quality submission data is outlined in this Guidance document based on the Schedule C drug's emission characteristics (GERs, PERs, NGNPs) or how the Schedule C drug is manufactured (generators, kits).

The extent of necessary quality information can vary with the stage of product development.

Note: The IB should provide relevant information on quality – see subsections below.

3.1.1. Gamma-emitting radiopharmaceuticals (GERs)

A gamma-emitting radiopharmaceutical (GER) is a Schedule C drug that contains a gamma emitter, is pre-radiolabelled as a final drug product and is supplied in a ready-to-use dosage form. The GER is not further manipulated prior to administration of the product in patients, other than to measure the radioactive dose, pH, and perform radiochemical purity (RCP) analysis, according to the IB.

Note on how to navigate 2 of the subsections that follow:

- If the GER contains a drug substance of chemical origin that is radiolabelled with a radionuclide, then both Section 3.1.1.2 - Drug substance synthesis and purification, and Section 3.1.1.3. - Radionuclide source and production apply;

and

- If the GER contains only the radionuclide or radiochemical, then only Section 3.1.1.3 - Radionuclide source and production applies e.g., when the GER is used in radiolabelling of a kit.

3.1.1.1. Source

With respect to source, the sponsor should:

- list the names and addresses of all facilities involved in the manufacture, packaging, labelling, and testing of the radionuclide, precursor or ligand, API or drug substance or both, and drug product.

3.1.1.2. Drug substance synthesis and purification

With respect to drug substance synthesis and purification, the sponsor should provide:

- a list of all raw materials, and a list of all starting materials, each of the materials with their C of A either from the vendor or generated in-house;
- details on synthesis, purification, and the structure elucidation process, including quality controls, specifications, and a flow chart identifying reaction yield;
- stability study data under accelerated and real-time storage conditions; a stability study could be an ongoing process for a first-time-in-human drug substance with, preferably, at least 3 months real-time study data;
- stability data for at least 1 full-scale batch;
- stability data generated at both upright and inverted orientations; or a rationale if data for only 1 orientation has been generated e.g, lyophilized pellet;

and

- the projected shelf-life and its supporting study conditions and study duration.

Packaging should follow all applicable standards for the product type.

Labelling must follow the regulatory requirements referenced in Section 6.3 - Key legal references.

3.1.1.3. Radionuclide source and production

With respect to radionuclide source and production, the sponsor should provide:

- information on the radionuclide synthesis process, including details about the cyclotron, accelerator, reactor, or generator used; when applicable, a DMF should be submitted or cross-referenced or both;
- detailed information on the target, including target body; information on other raw materials should be submitted if not included in the DMF;
- C of A for the target material either from the vendor or generated in-house;
- specifications of the radionuclide;
- analysis of radionuclidic, radiochemical, and chemical purity and impurity;
- analysis of target breakthrough in the final radionuclide (i.e., desired product) such as Mo-100 in Tc-99m made directly via cyclotron or accelerator;

and

- if the radionuclide is used in manufacturing to radiolabel ligands, then data should be generated for kits containing anionic, cationic, and neutral ligands if the radionuclide is intended to radiolabel kits or other ligands.

3.1.1.4. Development pharmaceutics

With respect to development pharmaceutics, the sponsor should provide any development work that was carried out, including formulation, batch size and strength, and its method of manufacture, to determine that the following are satisfactory for the intended use of the drug product:

- the radionuclide, API or drug substance, or radiopharmaceutical;

and

- any other ligand or precursor in the production of the final drug product.

3.1.1.5. Formulation and drug product manufacturing

With respect to formulation and drug product manufacturing, the sponsor should provide:

- a table identifying all ingredients and their roles in the formulation;
- detailed information on the manufacturing process, including radiolabelling, purification, vial filling, vial stoppering, and packaging;
- batch analyses data, and batch production records with release specifications for at least 3 pilot-scale, clinical-scale, or commercial-scale batches of the final product, depending on stage of drug development; additionally, the sponsor should indicate which tests are done prospectively, and which tests are done retrospectively;
- SOPs for all analytical procedures with their validation study data for Phase III CTAs; however for Phase I or II CTAs, the sponsor should instead provide:
    - summaries of analytical methods;

    and

    - summaries of applicable method validation (e.g., endotoxin, sterility, and filter integrity);

and

- shipping validation data covering the furthest distance simulating the real-life commercial supply; or if not possible, a statement that the end user is responsible for performing stability indicating tests i.e., the percentage of radiochemical purity, the pH, and the appearance of the final drug product as set out in the IB.

3.1.1.6. Stability and packaging

With respect to product stability and compatibility with packaging materials which are in direct contact with the drug product (e.g., vials, stoppers), the sponsor should provide stability data:

- for full-scale clinical trial batches using various real-time storage conditions;
- generated at both upright and inverted orientations;

and

- for at least 3 time points to support the recommended shelf-life that reflects study conditions and duration.

Packaging should follow all applicable standards for the product type.

Labelling must follow the regulatory requirements referenced in Section 6.3 - Key legal references.

3.1.1.7. Pharmaceutical comparability and equivalency

This section exists for ANDS only, and is not applicable to CTA nor NDS.

3.1.2. Positron-emitting radiopharmaceuticals (PERs)

A positron-emitting radiopharmaceutical (PER) is a Schedule C drug that contains a cyclotron-produced or accelerator-produced positron emitter, such as Carbon-11 (C-11), Nitrogen-13 (N-13), Oxygen-15 (O-15), or Fluorine-18 (F-18). One of the most common PERs is F-18 labelled Fluorodeoxyglucose (FDG).

Note:

- PERs that are manufactured using radionuclide generators are not addressed in Section 3.1.2 - Positron-emitting radiopharmaceuticals (PERs), but are addressed in Section 3.1.4 - Generators.

3.1.2.1. Source

With respect to source, the sponsor should:

- list the names and addresses of all facilities involved in the manufacture, packaging, labelling, and testing of the radionuclide, precursor or ligand, API or drug substance or both, and drug product.

3.1.2.2. Precursor, ligand, or drug substance source and synthesis

With respect to the source and synthesis of the precursor or ligand, the sponsor should indicate if the precursor or ligand is available commercially, synthesized in-house, or synthesized by a contract manufacturer.

If the precursor or ligand is a commercial product (e.g., mannose triflate), the sponsor should provide the name and C of A from the vendor, including storage conditions and expiry date.

Whether the precursor or ligand is synthesized by the sponsor or a contract manufacturer, the sponsor should provide:

- a list of all raw materials, and a list of all starting materials each with their C of A either from the vendor or generated in-house;
- details on synthesis, purification, structure elucidation process, and chemical reaction process of the precursor or ligand, including a flow chart with reaction yield, quality control, and specifications; if specifications are under development, the sponsor should provide the purity/impurity profile with other essential test parameters;
- stability data under real-time storage conditions for at least 3 months; alternatively, if stability data is not available, the sponsor should confirm that the study is ongoing and should provide a commitment to submit the data as soon as available;
- stability data for at least 1 full-scale batch;
- stability data generated at both upright and inverted orientations; or a rationale if data for only 1 orientation has been generated;

and

- the projected shelf-life and its supporting study conditions and study duration.

Packaging should follow all applicable standards for the product type.

Labelling must follow the regulatory requirements referenced in Section 6.3 - Key legal references.

3.1.2.3. Radionuclide source and production

With respect to radionuclide source and production, the sponsor should provide:

- information about the cyclotron used e.g., type, size or capacity, target size, target body type, beam current and irradiation time;
- detailed information on the target e.g., enrichment level, vendor name with the C of A;
- information on enrichment level and procedure with respect to whether the target is reused or recycled;
- information about the radionuclide production or synthesis process; when applicable, a DMF should be submitted or cross-referenced or both;
- information about other raw materials used for processing or purification beyond the scope of the DMF;
- specifications of the radionuclide, including acceptance limits of other radionuclidic impurities;

and

- in the case where the radionuclide is imported, information about the shipping process and further manufacturing, including details of the processing on receipt at the site prior to use in radiosynthesis.

3.1.2.4. Development pharmaceutics

With respect to development pharmaceutics, the sponsor should provide any development work that was carried out, including formulation, batch size and strength, and method of manufacture, to determine that the following are satisfactory for the intended use of the drug product:

- the radionuclide, API or drug substance, or radiopharmaceutical;

and

- any other ligand or precursor in the production of the final drug product.

3.1.2.5. Formulation and drug product manufacturing

With respect to formulation and drug product manufacturing the sponsor should provide:

- a quantitative formulation table for a batch and unit vial, including the radioactivity range (in MBq or mCi), identifying all ingredients and their roles in the formulation;
- details of the manufacturing process with respect to the Automated Synthesis Unit or Semi-Automated Synthesis Unit or manual radiolabelling; the deprotection and purification processes including radiochemical yield at the end of synthesis;
- details of the vial filling, stoppering, labelling, and packaging;
- for ASU or S/ASU, the type of cartridge or manifold used, and its vendor information;
- batch analyses data, and batch production records with release specifications for at least 3 pilot-scale, clinical-scale, or commercial-scale batches of the final product, depending on stage of drug development; additionally, the sponsor should indicate which tests are done prospectively, and which tests are done retrospectively;
- SOPs for all analytical procedures with validation study data for Phase III CTAs; however for Phase I or II CTAs, the sponsor should instead provide:
    - summaries of analytical methods;

    and

    - summaries of applicable method validation (e.g., endotoxin, sterility, and filter integrity);

and

- shipping validation data covering the furthest distance simulating the real-life commercial supply; or if not possible, a statement that the end user is responsible for performing stability indicating tests i.e., the percentage of radiochemical purity, the pH, and the appearance of the final drug product as set out in the IB.

3.1.2.6. Stability and packaging

With respect to product stability and compatibility with packaging materials which are in direct contact with the drug product (e.g., vials, stoppers), the sponsor should provide stability data:

- for a minimum of 1 pilot-scale, clinical-scale, or commercial-scale batch using various real-time storage conditions;
- generated at both upright and inverted orientations; or a rationale if data for only 1 orientation has been generated;

and

- for at least 3 time points to support the recommended shelf-life that reflects study conditions and duration.

Packaging should follow all applicable standards for the product type.

Labelling must follow the regulatory requirements referenced in Section 6.3 - Key legal references.

3.1.2.7. Pharmaceutical comparability and equivalency

This section exists for ANDS only, and is not applicable to CTA nor NDS.

3.1.3. Non-GERs non-PERs radiopharmaceuticals (NGNP)

A non-GERs non-PERs radiopharmaceutical (NGNP) is a Schedule C drug produced by a linear accelerator or nuclear reactor. NGNPs include alpha emitters and negatron emitters (beta minus). NGNPs include, but are not limited to, radionuclides such as Astatine-211 (As-211), Iodine-131 (I-131), Lutetium-177 (Lu-177), Radium-223 (Ra-223), Rhenium-188 (Re-188), Samarium-153 (Sm-153), Thorium-227 (Th-227), and Yttrium-90 (Y-90).

Note on how to navigate 2 of the subsections that follow:

- If the NGNP contains a drug substance of chemical origin that is radiolabelled with a radionuclide, then both Section 3.1.3.2 - Drug substance synthesis and purification, and Section 3.1.3.3 - Radionuclide source and production apply;

and

- If the NGNP contains only the radionuclide or radiochemical, then only Section 3.1.3.3 - Radionuclide source and production applies.

3.1.3.1. Source

With respect to source, the sponsor should:

- list the names and addresses of all facilities involved in the manufacture, packaging, labelling, and testing of the radionuclide, precursor or ligand, API or drug substance or both, and drug product.

3.1.3.2. Drug substance synthesis and purification

With respect to drug substance synthesis and purification, the sponsor should provide:

- a list of all raw materials, and a list of all starting materials each with their C of A either from the vendor or generated in-house;
- details on synthesis, purification, and the structure elucidation process, including quality controls, specifications, and a flow chart identifying reaction yield;
- a stability study, which is an ongoing process for a first-time-in-human drug substance. The sponsor should submit both data under accelerated storage conditions with at least 1 month study data, and data under real-time storage conditions with, preferably, at least 3 months study data;
- stability data for at least 1 full-scale batch;
- stability data generated at both upright and inverted orientations; or a rationale if data for only 1 orientation has been generated;

and

- the projected shelf-life and its supporting study conditions and study duration.

Packaging should follow all applicable standards for the product type.

Labelling must follow the regulatory requirements referenced in Section 6.3 - Key legal references.

3.1.3.3. Radionuclide source and production

With respect to radionuclide source and production, the sponsor should provide:

- information on the radionuclide synthesis process, including details about the cyclotron, accelerator, reactor, or generator used; when applicable, a DMF should be submitted or cross-referenced or both;
- detailed information on the target, including target body; information on other raw materials should be submitted if not included in the DMF;
- C of A for the target material from either the vendor or generated in-house;
- specifications of the radionuclide;
- analysis of radionuclidic, radiochemical, and chemical purity and impurity;
- analysis of target breakthrough in the final radionuclide (i.e., desired product) such as Te-131 in I-131, or W-188 in Re-188, or Re-185 in Re-186, produced by a linear accelerator;

and

- radiolabelling data if the radionuclide is intended to radiolabel kits or other ligands.

3.1.3.4. Development pharmaceutics

With respect to development pharmaceutics, the sponsor should provide any development work that was carried out, including formulation, batch size and strength, and its method of manufacture, to determine that the following are satisfactory for the intended use of the drug product:

- the radionuclide, API or drug substance, or radiopharmaceutical;

and

- any other ligand or precursor in the production of the final drug product.

3.1.3.5. Formulation and drug product manufacturing

With respect to formulation and drug product manufacturing, the sponsor should provide:

- a quantitative formulation table for a batch and unit vial, including the radioactivity range (in MBq or mCi), identifying all ingredients and their roles in the formulation;
- detailed information on the manufacturing process, including radiolabelling, purification, vial filling, vial stoppering, and packaging;
- quality control and batch analyses data of the final product; additionally, the sponsor should indicate which tests are done prospectively, and which tests are done retrospectively;
- SOPs for all analytical procedures with their validation study data for Phase III CTAs; however for Phase I or II CTAs, the sponsor should instead provide:
    - summaries of analytical methods;

    and

    - summaries of applicable method validation (e.g., endotoxin, sterility, and filter integrity);

and

- shipping validation data covering the furthest distance simulating the real-life commercial supply; or if not possible, a statement that the end user is responsible for performing stability indicating tests i.e., the percentage of radiochemical purity, the pH, and the appearance of the final drug product as set out in the IB.

3.1.3.6. Stability and packaging

With respect to product stability and compatibility with packaging materials which are in direct contact with the drug product (e.g., vials, stoppers), the sponsor should provide stability data:

- for full-scale clinical batches using various real-time storage conditions;
- generated at both upright and inverted orientations;

and

- for at least 3 time points to support the recommended shelf-life that reflects study conditions and duration.

Packaging should follow all applicable standards for the product type.

Labelling must follow the regulatory requirements referenced in Section 6.3 - Key legal references.

3.1.3.7. Pharmaceutical comparability and equivalency

This section exists for ANDS only, and is not applicable to CTA nor NDS.

3.1.4. Generators

A generator is defined in Part C, Division 3 of the *Food and Drug Regulations* (C.03.001).

A generator typically contains a column with a large amount of a radionuclide (i.e., parent radionuclide) that decays down to a second radionuclide of shorter half-life (i.e., daughter radionuclide). The daughter radionuclide is separated from the parent by the process of elution, which gives a continuing supply of relatively short-lived radionuclides.

3.1.4.1. Source

With respect to source, the sponsor should:

- list the names and addresses of all facilities involved in the manufacture, packaging, labelling, and testing of the radionuclide, precursor or ligand, API or drug substance or both, and drug product.

3.1.4.2. Parent radionuclide and processing

With respect to the parent radionuclide and its processing, the sponsor should provide:

- general information about the production, properties, and quality control of the parent radionuclide e.g., C of A for radionuclidic, radiochemical, and chemical purity and impurities, specific activity, activity concentration, pH, appearance, etc. Alternatively, the sponsor may cross-reference to an existing file with a letter of authorization from the owner of that file;
- detailed information about the accelerator or reactor used. Alternatively, the sponsor should cross-reference a DMF;

and

- detailed information about the target or target body. Additionally, the sponsor should provide detailed information about other raw materials when not included in the DMF.

3.1.4.3. Development pharmaceutics

With respect to development pharmaceutics, the sponsor should provide any development work that was carried out to determine that the following are satisfactory:

- the parent radionuclide e.g., its amount, column type and length, adsorbent material and its amount, other materials used in the production of the generator including its formulation and batch size;

and

- the parent radionuclide's method of manufacture.

3.1.4.4. Formulation and generator manufacturing process

With respect to formulation and generator manufacturing process, the sponsor should provide:

- the names and addresses of all facilities involved in the production and processing of the parent radionuclide and the generator;
- the formulation and production methodology of the generator, including total radioactivity of the generator, type and source of adsorbent, tubing, sterile filter, collection vial etc.;
- in the case where the eluate is for direct administration, details about dose preparation i.e., volume, specific activity, total radioactivity, radioactive concentration, and other appropriate data;
- specifications for the final product (i.e., the eluate) which should at least include appearance, radionuclidic purity, radiochemical purity, percentage of parent radionuclide breakthrough or radioactive amount present (in MBq or mCi) and the amount of adsorbent material present, pH, and when applicable, osmolality;
- confirmation of which quality control test parameters are done at release, and which are done retrospectively;
- complete batch analysis data, including data for tests done retrospectively, for clinical trial batches;
- SOPs for all analytical procedures with their validation study data for Phase III CTAs; however for Phase I or II CTAs, the sponsor should instead provide:
    - summaries of analytical methods;

    and

    - summaries of applicable method validation (e.g., endotoxin, sterility, and filter integrity);

and

- in the case where the daughter radionuclide radiolabels kits or other ligands, radiolabelling data for kits containing anionic, cationic, and neutral ligands. If the radionuclide is only to be used to radiolabel a specific kit or ligand, then the sponsor should provide radiolabelling data for that particular kit or ligand.

3.1.4.5. Stability and packaging

With respect to stability and packaging, the sponsor should provide for at least 3 pilot-scale, clinical-scale, or commercial-scale batches of the final product, depending on stage of drug development:

- data to support generator stability for the column, including for parent radionuclide and column adsorbent breakthrough throughout the shelf-life of the generator, and its eluate specifications for percentage of radiochemical purity, percentage of radionuclidic purity, pH, and appearance;
- data to support the expiry date of the eluate at post-elution, including storage conditions;
- data to support stability associated with compatibility of the vial content with the container closure i.e., a study performed by storing at the upright and inverted orientations for up to the proposed expiry period;

and

- information that shows that packaging is according to generator type and size with required shielding as specified by the CNSC.

Packaging should follow all applicable standards for the product type.

Labelling must follow the regulatory requirements referenced in Section 6.3 - Key legal references.

3.1.4.6. Pharmaceutical comparability and equivalency

This section exists for ANDS only, and is not applicable to CTA nor NDS.

3.1.5. Kits

A kit is defined in Part C, Division 3 of the *Food and Drug Regulations* (C.03.205).

A kit is a Schedule C drug that is used in the preparation of a radiopharmaceutical.

3.1.5.1. Source

With respect to source, the sponsor should:

- list the names and addresses of all facilities involved in the manufacture, packaging, labelling, and testing of the API or drug substance, and drug product.

3.1.5.2. Drug substance synthesis and purification

With respect to drug substance synthesis and purification, the sponsor should provide:

- a list of all raw materials, and a list of all starting materials each with their C of A either from the vendor or generated in-house;
- details on synthesis, purification, and the structure elucidation process, including quality controls, specifications, and a flow chart identifying reaction yield;
- stability data under accelerated and real-time storage conditions;
- the DMF obtained from the supplier, in the case where the drug substance is manufactured by a contract manufacturer;

and

- shipping validation data in the case where the product is shipped from off-site, including specific shipping information for thermolabile or photosensitive products.

3.1.5.3. Development pharmaceutics

With respect to development pharmaceutics, the sponsor should provide any development work that was carried out to determine that the following are satisfactory:

- the drug substance, excipients, and radionuclide(s) used in reconstitution;
- their amounts;

and

- any other materials used in the preparation of the final drug product, including its formulation, batch size and strength, and its method of manufacture.

3.1.5.4. Formulation and drug product manufacturing

With respect to formulation and drug product manufacturing, the sponsor should provide:

- a table identifying all ingredients and their roles in formulation;
- detailed information on the manufacturing process, including purification, vial filling, vial stoppering, lyophilization, and packaging;
- batch analyses data, and batch production records that include release specifications for the radiolabelling method and analysis of percentage of radiochemical purity and impurities for the following 3 situations:

- using a radionuclide from a source approved in Canada or an eluate from a generator approved in Canada;
- obtaining Tc-99m or other gamma-emitting radionuclides from a generator. In this situation, the sponsor should additionally provide data that demonstrates that conditions, such as when the eluate is more than 2 hours old and from a generator not eluted for more than 72 hours, do not affect the desired radiolabelling yield, nor the radiochemical purity and impurity profiles;

or

- obtaining radionuclides other than Tc-99m from a generator (e.g., Re-186). In this situation, the sponsor should additionally provide data that demonstrates that conditions do not affect the desired radiolabelling yield, nor the radiochemical purity and impurity profiles e.g., placing limits on the expiry of the eluate related to when the generator was last eluted, or when the generator is not eluted in the specified time;
    - If conditions are not met, the sponsor should state in the IB the generator-specific conditions with the eluate-specific conditions, such as the eluate is not over 2 hours old from a generator eluted within the last 24 hours;

and

- SOPs for all analytical procedures with their validation study data for Phase III CTAs; however for Phase I or II CTAs, the sponsor should instead provide:
    - summaries of analytical methods;

    and
    - summaries of applicable method validation (e.g., endotoxin, sterility, and filter integrity).

3.1.5.5. Stability and packaging

With respect to stability and packaging, the sponsor should provide:

- stability data for full-scale batches, for real-time storage conditions for the drug product (cold kit);
- stability data for full-scale batches for the final radiolabelled drug product;
- study data generated at both upright and inverted orientations for the cold kit and the final radiolabelled drug product;

and

- data for at least 3 time points to support the recommended shelf-life that reflects study conditions and duration, for both:
    - the drug product (cold kit);

and

- the final radiolabelled drug product.

Packaging should follow all applicable standards for the product type.

Labelling must follow the regulatory requirements referenced in Section 6.3 - Key legal references.

3.1.5.6. Pharmaceutical comparability and equivalency

This section exists for ANDS only, and is not applicable to CTA nor NDS.

3.2. NON-CLINICAL SUBMISSION DATA

This introduction provides sponsors with key general information that underlies the specific non-clinical submission data requested in the non-clinical subsections below.

Non-clinical submission data is outlined in this Guidance document for all Schedule C drugs, regardless of how the drug is used (e.g., diagnostic or therapeutic). When there are differences in submission data for diagnostic and therapeutic radiopharmaceuticals, they are set out.

- Diagnostic radiopharmaceuticals are used to diagnose, monitor, or determine the stage of a disease or condition. Clinical treatment platforms are structured for these specific clinical indications, therefore many standardized principles and guidelines for clinical study design, conduct, data processing and analysis apply to diagnostic radiopharmaceuticals.
- Therapeutic radiopharmaceuticals are used to treat or manage a disease or condition. The drug development cascade and clinical platforms and expectations for other therapeutic drug products (i.e., pharmaceuticals or biologics) typically apply to therapeutic radiopharmaceuticals.

Goals: The primary goals of a non-clinical safety evaluation for Schedule C drugs are the same as for all drugs, and should include:

- to identify safe dose ranges, and subsequent dose exposure in humans;
- to identify potential target organs for toxicity, and for the study of whether such toxicity is reversible;
- to identify safety parameters where clinical monitoring may be needed;

and

- to assess biological, physical, and effective half-life considerations and critical dose organs that impact the radiation dosimetry estimates and evaluation.

Studies: Non-clinical, single-dose, toxicity studies should be completed before the first introduction of the drug into humans. These studies should examine at least a 100X greater dose than the maximal anticipated human mass dose. Most radiopharmaceuticals

can be administered at a low mass dose of the ligand for an intended single dose, or a very limited number of repeated single doses. When the mass dose is administered at the low end of a dose-response curve, dose-related pharmacologic effects, or adverse events associated with a pharmacologic effect, are less likely to occur. Typically, all non-clinical studies can be conducted with non-radiolabelled material, except for biodistribution studies.

Biological activity: Biological activity jointly with tissue specificity should be taken into account in standard toxicity testing designs, depending on the choice of animal species or when the ligand is a biologic (e.g., monoclonal antibody). Non-clinical studies should use relevant species, when applicable, where the test material is pharmacologically active as a result of the expression of the receptor (e.g., as with monoclonal antibodies). Animal species that do not express the desired epitope may be relevant if comparable tissue cross-reactivity to humans is demonstrated.

Product formulation: The product formulation used in non-clinical studies and safety margin estimations should ideally be the same formulation intended for use in clinical trials and the marketplace. If the product formulation changes during product development, a rationale, and potentially bridging data, should be generated to substantiate the data linkages with the different formulations. Bridging data should be used when formulation changes could result in altered pharmacokinetics or pharmacodynamics (hence potentially altered radiation dosimetry), or overall safety considerations. Bridging data should help facilitate comparisons between data sets and formulations, especially if there have been changes between the species or animals used in non-clinical or clinical studies, or both.

Toxicology: Drug product components should be considered in the toxicological assessment e.g., non-medicinal ingredients, excipients, impurities, etc. Components may need specific and detailed testing individually if toxicological data is generally lacking. Individual component studies are not usually required if testing is performed on combined components and results are unremarkable. When undertaken, genotoxicity of the non-radioactive component should be conducted separately so as to distinguish it from that of the radionuclide. When the mass dose administered is at the low end of the dose-response curve (e.g., micro-dose), certain elements of the toxicological assessment (e.g., genotoxicity and mutagenicity) may not be required if supported by a rationale provided by the sponsor.

General: The non-clinical study component of development should be based on sound scientific and clinical principles and should be linked with the proposed product's unique properties (taking into account the ligand and radionuclide) and intended clinical use(s). The number and types of non-clinical studies depend on stage of development and information already known about the constituents, including the pharmacologic profile, intended use, and target patient population.

Specifics - additional information for diagnostic radiopharmaceuticals:

- Long-term repeat-dose toxicity non-clinical studies are not typically required for diagnostic radiopharmaceuticals due to their typical characteristics and patterns of intended use. Long effective half life is an example of an exception.
- Studies of long-term carcinogenicity and developmental and reproductive toxicity are not typically undertaken unless there are indicators from rodent and non-rodent short-term toxicity studies e.g., embryonic and fetal toxicities that increase the uncertainty of reproductive and developmental risk.

Specifics - additional information for therapeutic radiopharmaceuticals is based on the intended nature of these products as a therapeutic intervention in a treatment capacity, thus delivering a therapeutic absorbed radiation dose:

- In instances of fractionated dosing, repeated dose exposure should be typically done at specific intervals for a targeted cumulative dose. When repeat divided dosing involves a radiopharmaceutical that consists of a biologic ligand, the immunogenic potential should be considered, and the immunogenicity profile should be examined and characterized.
- The effect on radiation dosimetry of variations in biodistribution results or product design (e.g., specific receptor or organ targets) should be investigated in order to help characterize the safety profile of the drug, because change in radiation dosimetry may occur in the presence of diseases in organs related to metabolism or excretion.
- The effect on radiation dosimetry of variations in receptor mass or antigen burden should be investigated in order to facilitate optimal dose range or dose-characterizing studies in patients.

Note for the Non-clinical sub-sections that follow: A summary of the studies that support product safety would be outlined in the IB. Raw data would not typically be submitted in the CTA. Health Canada may request non-clinical reports on a case-by-case basis.

3.2.1. Pharmacology

3.2.1.1. Primary pharmacodynamics

With respect to primary pharmacodynamics, the sponsor should provide as a summary in the IB:

- studies that characterize mode of action with respect to its desired effect.

Additional information for diagnostic radiopharmaceuticals: These types of studies should reflect groupings of intended diagnostic use, and may relate to anatomic structure delineation; or functional, physiological, or biological evaluation.

Additional information for therapeutic radiopharmaceuticals: These types of studies should reflect groupings of intended therapeutic use for conditions or disease states.

3.2.1.2. Secondary pharmacodynamics

With respect to secondary pharmacodynamics, the sponsor should provide as a summary in the IB:

- studies that address one or both modes of action, or effects of the product not related to the product's diagnostic capabilities, or therapeutic effect. These considerations may be pertinent to safety.

3.2.1.3. Safety pharmacology

With respect to safety pharmacology, the sponsor should provide as a summary in the IB:

- safety pharmacology studies that investigate the potential effects of the test material on vital functions in core organ systems, such as cardiovascular (including QT prolongation studies), respiratory, and central nervous systems.

Generally for diagnostic radiopharmaceuticals, safety pharmacology studies are not necessary. Some elements can be examined on a limited basis through toxicology studies.

Additional information for therapeutic radiopharmaceuticals:

- prior to first in-human exposure, safety pharmacology studies should also include a focus on major organs or organ systems that the therapeutic radiopharmaceutical is intended to target;

and

- other safety studies that investigate the effect of the test material on other organ systems, based on the pharmacological activity profile of the ligand associated with the product. These organ systems include, for example, renal/urinary, autonomic nervous, gastro-intestinal, muscle, immune, endocrine systems.

3.2.2. Pharmacokinetics

This introduction provides sponsors with key general information that underlies all specific non-clinical submission data requested in the subsections that follow.

Pharmacokinetic studies should use, when possible:

- preparations representative of intended toxicity testing and clinical use;

and

- the route of administration in anticipated clinical studies.

When using radiolabelled ligands, it should be shown that radiolabelled material maintains biological properties and receptor affinity equivalent to that of the un-radiolabelled material.

- For the therapeutic radioactive dose, this can be particularly relevant, given the larger activity amounts that are administered.
- For diagnostic agents that have a different chemical structure than their precursor, the unlabelled ligand may not be relevant for study e.g., labelled compounds where the structural contribution from the radionuclide is integral to biological properties.

3.2.2.1. Analytical methods and validation

With respect to analytical methods and validation, the sponsor should provide a summary of:

- evidence that methods are validated according to standard procedures for quantitative analytical assay performance.

3.2.2.2. Absorption, distribution, metabolism, excretion

With respect to absorption, distribution, metabolism, and excretion, the sponsor should provide as summary in the IB:

- a characterization of the disposition (distribution and elimination) of the radiolabelled compound, including the nuclear physics, mode of decay etc., of the radionuclide.

Note:

- Characterization is requested because biological, physical, and effective half-lives are incorporated into radiation dosimetry estimates and evaluations.
- The nuclear physics, mode of decay etc., of the radionuclide should be used in non-clinical-to-clinical exposure estimations for absorbed radiation doses (i.e., radiation dosimetry) prior to characterization in humans. Such estimates of absorbed dose establish the dosing platform for both first clinical exposures and further clinical trials that assess safety and efficacy in patients.

3.2.3. Radiation dosimetry

This introduction provides sponsors with key general information that underlies the radiation dosimetry specific submission data requested in the subsections below.

With respect to radiation absorbed dose estimates, the sponsor should provide as a summary in the IB:

- pre-clinical animal data for radiation absorbed dose estimates to support first in human administration;

and

- the actual biodistribution and radiation absorbed dose resulting from the recommended amount of administered radioactivity. This information is unique to each radiopharmaceutical product.

The sponsor should also demonstrate there is:

- sufficient data from animal studies to be able to refine dose selection when the product is later administered to a patient, so that the radiation absorbed dose estimates can be characterized and confirmed from actual human data;

and

- the rationalization for dose selection and the verification of nominal choice for the activity to be administered, with the safety/benefit profile of the product under conditions of clinical use.

For submission information in the next stage of development, continue onwards to the CTA Clinical section, Section 3.3, in this Guidance.

3.2.3.1. Biodistribution, corroborating data, assumptions, and models

With respect to biodistribution and corroborating data for radiation absorbed dose estimates, the sponsor should provide as a summary in the IB:

- all sources of data from animal biodistribution studies used to calculate radiation absorbed dose estimates;
- a description of models used to calculate radiation absorbed dose estimates;

and

- an analysis of all assumptions used in any dose calculation.

With respect to radiation absorbed dose estimates in animal models, the sponsor should provide as a summary in the IB:

- a summary of dose estimates;
- a presentation of corroborating data (parameters, assumptions, models, etc.) used to calculate the dose estimates;
- dose estimates calculated from biodistribution data;

and

- estimates of the equivalent dose or the effective dose or both, per unit administered activity (mSv/MBq and mrem/mCi) for each phantom.

The sponsor should provide, as a summary in the IB, the characterization of radiation dosimetry:

- a summary of dose estimates;

and

- a presentation of corroborating data (parameters, assumptions, models, etc.) used to calculate the final dose estimates.

Presentation of the raw data used to derive the parameters should be available upon request.

3.2.3.2. Summary of radiation dose estimates

With respect to radiation absorbed dose estimates, the sponsor should provide as a summary in the IB overall radiation dose estimates that include:

- the radionuclide used in the formulation of the drug (i.e., the principal radionuclide);

and

- any radiochemical or radionucludic impurities that may contribute substantially to the total effective dose.

These inclusions can help characterize the absorbed dose that may be impacted by such impurities, and is a means to help account for contributions to the total radiation burden e.g., effective dose.

3.2.3.3. Presentation of data

This section exists for Clinical CTA and Clinical NDS only, and is not applicable to Non-clinical CTA.

3.2.4. Toxicology

This introduction provides sponsors with key general information that underlies the toxicology specific submission data requested in the subsections below.

Most diagnostic radiopharmaceuticals can be administered at a low mass dose of the ligand for a single dose, or a very limited number of repeated single doses. When the mass dose is administered at the low end of a dose-response curve (e.g., micro-dose administration), dose-related pharmacologic effects or adverse events associated with a pharmacologic effect are less likely to occur. Multiple dose levels greater than those for clinical use are used in toxicology studies.

Assessment may include a non-radioactive component or the radiolabelled compound or both. Therefore the design of toxicology studies should take into account the radiopharmaceutical's biological and physical half-lives. The studies can be done using the ligand, or the radiopharmaceutical after it is has decayed. In the case of therapeutic radiopharmaceuticals, the radiolabelled compound is preferred in order to assess the late radiation toxicity.

A distinction is also made between ligands of biological and chemical origins. Specific guidance for biologics should also be taken into account where needed. Biological

ligands are usually large molecules i.e., peptides or proteins. Many are species-specific and engineered for human use, thus may cause formation of anti-drug antibodies or neutralizing antibodies that could interfere with the conduct of animal studies. In these cases, use of a homologous protein may be considered. Immunogenicity is a toxicological and safety concern when a biologic is the ligand and should be investigated. Products with a biologic as the ligand typically require consideration on a case-by-case basis. Standard toxicity testing protocols may not always be appropriate for such biotechnology products, and instead the parameters may utilize studies that incorporate alternate or specialized test parameters, such as transgenic or animal versions of human protein and disease models.

With respect to single dose or repeat dose studies, the sponsor should provide as a summary in the IB:

- data from preferably 2 relevant mammalian species, rodents and non-rodents. Alternatively, when not possible in the case of biologic ligands, the sponsor should provide data from 1 relevant mammalian species;
- data that demonstrates an adequate number of animals were used for valid statistical analysis. When not possible in the case of non-human primates, the sponsor should provide a justification for restricted sample size;
- evidence from evaluations done after the exposure that assess any delay of toxicity and monitor for any recovery;
- data that demonstrates that both sexes are tested. Alternatively, the sponsor should provide a justification for why only 1 sex is tested;
- data that demonstrates sufficient multiples of dose levels for the intended clinical maximal mass dose;
- data that demonstrates the level of exposure of test material on test animals, relative to clinical exposure to humans;

and

- immunogenicity data in the case of biologic ligands for toxicology safety reasons.

3.2.4.1. Single-dose acute toxicity studies

With respect to single-dose studies and acute toxicity, the sponsor should provide as a summary in the IB:

- the species, number, sex, weights, and strains of animals;
- information on dosage, formulation, routes of administration, and duration of treatment;
- methodology;
- parameters evaluated in clinical observations (e.g., vital signs, local tolerance etc.);
- hematology, clinical chemistry, and histopathology;
- any other pertinent information;
- further to study protocol, the above information presented separately for animals sacrificed during and at the end of the 14-day observation

period e.g., extended single-dose studies to assess for maximum effect and recovery;
- endpoints (e.g., non-lethal dose, no toxic effect level) with their ratios to the proposed maximal human mass dose;
- data that demonstrates the NOAEL, by using multiple dose levels of 100X or greater than the mass dose intended for clinical use;

and
- study conclusions.

Sponsors should follow guidelines on GLPs set out in Section 6.4.1.1 – World Health Organisation (WHO).

3.2.4.2. Repeat-dose studies

With respect to repeat-dose studies evaluating multiple-dose toxicity, the sponsor should provide as a summary in the IB each study including:
- the species, number, sex, weights, and strains of animals;
- information on dosage, formulation, routes of administration, and duration of treatment;
- methodology;
- parameters evaluated in clinical observations (e.g., vital signs, local tolerance etc.);
- hematology, clinical chemistry, and histopathology;
- any other pertinent information;
- results, such as the nature and severity of target organ toxicity, dose exposure-response relationships, or differences between species, gender, etc.;
- evidence from evaluations done after the recovery period, that assess reversibility of any toxicological effects and the potential for delayed toxicity;
- data that demonstrates the NOAEL after using multiple dose levels greater than the mass dose intended for clinical use;
- further to study protocol when relevant, estimates of the maximal tolerated doses for specific toxic effects and their relationship to the proposed maximum human dose;

and
- study conclusions.

Sponsors should follow guidelines on GLPs set out in Section 6.4.1.1 – World Health Organisation (WHO).

3.2.4.3. Genotoxicity and mutagenicity

With respect to genotoxicity and mutagenicity, the sponsor should provide, as a summary in the IB, 2 sets of data for separately conducted genotoxicity studies addressing:

- the non-radioactive component;

and

- the radionuclide;

in order to distinguish the effect of the non-radioactive component from that of the radionuclide.

When the mass dose administered is at the low end of the dose-response curve (e.g., micro-dose) or when the ligand is a biologic, certain elements of the toxicological assessment may not be required when supported by a rationale provided by the sponsor as a summary in the IB.

3.2.4.4. Carcinogenicity

Unless specifically requested by Health Canada, the sponsor can omit long-term animal studies that evaluate carcinogenic potential if supported by a rationale. For diagnostic purposes, the radiopharmaceutical dose is typically only a trace amount. For therapeutic purposes, depending on intended use and product type (e.g, alpha or beta emitters), alternate methodologies for determining carcinogenic potential may be appropriate.

Product-specific assessment of carcinogenic or mutagenic potential may still be necessary for diagnostic and therapeutic radiopharmaceuticals, depending upon clinical dosing, patient population or biological activity of the product or both.

- In particular for therapeutic radiopharmaceuticals, the sponsor should address the risk of mutagenic and carcinogenic effects because there is an increased exposure to ionizing radiation. Literature sources may be acceptable.

3.2.4.5. Reproductive and developmental toxicities

With respect to reproductive and developmental toxicities,

- in the case of diagnostic radiopharmaceuticals: the sponsor can generally omit reproductive toxicity non-clinical studies because of their typical characteristics and patterns of intended use.
    - However, in exceptional cases, such as for long effective half-life considerations, the sponsor should provide as a summary in the IB, data from short-term toxicity studies in rodents and non-rodents where limited embryonic and fetal toxicities are a related component. If these studies in exceptional cases are not conducted, the sponsor should include a rationale in the IB.

- in the case of therapeutic radiopharmaceuticals: the sponsor should provide data from reproductive and developmental toxicity studies that evaluate the risk of reproductive and developmental effects, because there is an increased radiation exposure compared with diagnostic radiopharmaceuticals.

3.2.4.6. Other information

In addition to the submission data requested above, the sponsor may provide, as a summary in the IB, other information to support their toxicity studies e.g., ,

- data from additional studies that assess the toxicological profile of the test material e.g., ligand-receptor binding studies, cross-reactivity studies, and a QT prolongation study;
- data from original articles published in peer-reviewed journals and sourced from multiple labs, research centres, or academic centres i.e., published data that is valid and supported by the scientific community. The data should be supportive of submissions (e.g., pharmacology, pharmacokinetics, toxicology, radiation dosimetry estimates etc.), and should represent a raw material of interest (i.e., associated with the drug substance or ligand), since such data is not usually generated for the specific formulation under development (i.e., the drug product);

or

- data with the specific drug development process taken into account, as differences in manufacturing and production may have an impact on quality.

3.3. CLINICAL SUBMISSION DATA

This introduction provides sponsors with key general information that underlies all specific clinical submission data requested in the clinical subsections below.

Clinical submission data is outlined in this Guidance document based on the clinical use of the Schedule C drug.

There are 2 types of Schedule C drugs with respect to clinical submission data: diagnostics and therapeutics.

- Diagnostic radiopharmaceuticals are used to diagnose, monitor, or determine the stage of a disease or condition. Clinical treatment platforms are structured for these specific clinical indications, therefore many standardized principles and guidelines for clinical study design, conduct, data processing and analysis apply to diagnostic radiopharmaceuticals.
- Therapeutic radiopharmaceuticals are used to treat or manage a disease or condition. The drug development cascade and clinical platforms and expectations for other therapeutic drug products (i.e., pharmaceuticals or biologics) typically apply to therapeutic radiopharmaceuticals.

All information in the Clinical subsections apply to both diagnostic and therapeutic radiopharmaceuticals unless otherwise indicated.

Most radiopharmaceuticals are initially designed for the adult patient population. When a radiopharmaceutical is developed for pediatric use, appropriate age groups and patient populations should be considered with respect to radiation absorbed dose and other development components.

The sponsor should provide the IB, the protocol, and the consent forms in the clinical data package. The sponsor should provide in the IB, where applicable, any available information regarding radiation dosimetry, pharmacokinetics, drug safety, pharmacodynamics, efficacy, and dose responses obtained from previous clinical trials in humans. This data can be sourced from literature where appropriate. The clinical subsections that follow, 3.3.1 to 3.3.4. inclusive, provide that direction.

3.3.1. Pharmacodynamics and pharmacology

3.3.1.1. Primary pharmacodynamics

With respect to primary pharmacodynamics, the sponsor should provide as a summary in the IB:

- data from Phase I first in-human exposure studies that gather pharmacokinetic and initial safety assessments of the estimated mass dose and biodistribution of the product.

Pharmacodynamic aspects should be incorporated in Phase I studies when the product is intended to target specific receptors, metabolic processes, or other high affinity tissues or organs.

For diagnostics: Healthy volunteers may be studied in Phase I studies, unless toxicity or the radiation dose precludes such exposures.

For therapeutics: Patients with the disease or condition to be treated are studied in all phases of clinical trials because toxicity or radiation dose preclude such exposures to healthy subjects.

3.3.1.2. Secondary pharmacodynamics

With respect to secondary pharmacodynamics, the sponsor should provide, as a summary in the IB, evidence that pharmacokinetics, pharmacodynamics, and dose exposure-response relationships:

- support dose selection, including of the ligand where appropriate; and
- substantiate any claims for a distinct lack of pharmacological effect

- for diagnostics: in mass or activity for those doses;

or

- for therapeutics: of the ligand or lack of an adverse profile.

3.3.1.3. Pharmacology

With respect to pharmacology, the sponsor should provide as a summary in the IB:

- Phase II studies that verify the dosage regimen characterization, which are the clinically relevant and useful mass dose and radiation activity dose range claimed to be clinically useful and studied in later trials.

Note:

- Phase II studies should contribute to the pharmacokinetics and pharmacodynamics characterization, and allow opportunity to refine timing, techniques, and processes
  - for diagnostics: imaging;

  or
  - for therapeutics: fractionated therapy as relevant.
- Preliminary evidence should be collected about the safety and efficacy in patients.
- For diagnostics:
  - it is relevant to include subjects with and without known disease in order to help establish diagnostic performance;

  and
  - technical imaging quality should be studied.

3.3.2. Pharmacokinetics

3.3.2.1. Analytical methods and validation

With respect to analytical methods and validation, the sponsor should provide as a summary:

- information on the bioanalytical methods and validations used to assess concentrations of ligands or other components etc., in biological matrices;

and

- information on the methods used to assess radiation quantifications.

3.3.2.2. Absorption, distribution, metabolism, excretion

With respect to absorption, distribution, metabolism, and excretion of the drug product, the sponsor should provide as a summary in the IB:

- sufficient data from human biodistribution studies;

and

- sufficient data from internal dosimetry modelling;

to allow an estimation of radiation absorbed dose to the whole body and critical organs when the drug is administered.

With respect to biodistribution characterization, the sponsor should provide, as a summary in the IB, the assumptions and methodology used, including all sources of data, with detailed descriptions of models used in dosimetry calculations supporting dosing levels.

The sponsor should explain all considerations made for anticipated changes in dosimetry resulting from the presence of disease (e.g., renal dysfunction leading to a decreased renal excretion or hepatic dysfunction leading to a change in hepatobiliary clearance or other compensatory changes in paths of elimination).

- Note: specific patient populations may need to be studied to allow a claim for use in a specific patient population with an altered condition (e.g., use in renal failure).

The sponsor should provide, as a summary in the IB in table format, all relevant physical and biological parameters used in calculating each organ dose for all target organs and critical organs (organs at risk). Examples of parameters are:

- the fractional uptake of administered radioactivity into each organ;
- the biological half-life in each organ;
- the contribution to absorbed dose from the principal radionuclide and all relevant radiochemical and radionuclidic impurities as presented by the sponsor's data and computations. Data should typically reflect that of an average adult human after the administration of the recommended radioactive dose (activity) of the radiopharmaceutical.

The sponsor should list operational definitions and verify corresponding units of expression when citing terminology, value declarations, or units of expression e.g., equivalent dose versus effective dose data presentations.

3.3.3. Radiation dosimetry

This introduction provides sponsors with key general information that underlies the radiation dosimetry specific submission data requested in the subsections below.

When radiation dosimetry estimates in humans are not available, the sponsor may use nonclinical studies to produce a reasonable estimation of radiation absorbed dose to the whole body and critical organs in humans.

The radiation absorbed dose estimates characterized from human data are then used to substantiate and verify the safety and efficacy profile which characterizes the conditions of use of the product.

In certain circumstances when sufficient original data is not available, the above requirements may instead be addressed by other means e.g., third-party data.

These situations would be assessed on a case-by-case basis.

With respect to providing radiation dosimetry estimates in humans, the sponsor should use the MIRD schema to estimate the absorbed dose (i.e., the concentration of energy deposited in the tissue or organ) in each organ or tissue. The sponsor:

- may refer to the most recent ICRP guidance on MIRD schema for dosimetry calculation;
- should use the most recent updated data on tissue and radiation weighting factors and nuclear decay data as per ICRP;
- should consider using reference phantoms for dosimetry calculation as recommended by ICRP;

and

- should consider using models and software that incorporate the most recent changes from ICRP e.g., the latest version of OLINDA/EXM.

The sponsor should also provide, as a summary in the IB, data for the maximum and minimum recommended dose/activity, including instances when dosing is individualized on a per metres squared or per kg basis.

3.3.3.1. Biodistribution, corroborating data, assumptions, and models

With respect to biodistribution and corroborating data for radiation absorbed dose estimates, the sponsor should provide as a summary in the IB:

- all sources of data from animal biodistribution studies used to calculate radiation absorbed dose estimates;
- a description of models used in radiation absorbed dose estimates calculations;

and

- an analysis of all assumptions used in any dose calculation.

With respect to radiation absorbed dose estimates in animal models, the sponsor should provide as summary in the IB:

- a summary of dose estimates;
- a presentation of corroborating data (parameters, assumptions, models, etc.) used to calculate the dose estimates;
- dose estimates calculated from biodistribution data;

and

- estimates of the equivalent dose or the effective dose or both, per unit administered activity (mSv/MBq and mrem/mCi) for each phantom.

With respect to the characterization of radiation dosimetry, the sponsor should provide as a summary in the IB:

- a summary of dose estimates;

and

- a presentation of corroborating data (parameters, assumptions, models, etc.) used to calculate the final dose estimates.

Presentation of the raw data used to derive the parameters should be available upon request.

3.3.3.2. Summary of radiation dose estimates

With respect to radiation absorbed dose estimates, the sponsor should provide as a summary in the IB:

- dose estimates based on human data used in the calculations, or extrapolated estimates from the supportive animal data included in the non-clinical section;
- estimates of the equivalent dose (i.e., how much biological change is expected from the absorbed dose). Note that the radiation weighting factor equals 1 for gamma and beta emitters;
- data estimates when phantoms are used;

and

- the effective dose (i.e., to assess the potential for long-term effects that might occur in the future) per unit administered activity (mSv/MBq and mrem/mCi).

Note that the effective dose is a calculated value that takes into account the absorbed dose to all organs of the body, the relative harm level of the radiation, and the sensitivities of each organ to radiation. It may be used to assess comparative radiation exposure.

The sponsor should provide as a summary in the IB overall radiation dose estimates that include:

- the radionuclide used in the formulation of the drug (i.e., the principal radionuclide);

and

- any radiochemical or radionucludic impurities that may contribute substantially to the total effective dose.

These inclusions can help characterize the absorbed dose that may be impacted by such impurities, and is a means to help account for contributions to the total radiation burden e.g., effective dose.

In the case of hybrid imaging with PET/CT or SPECT/CT, the sponsor should provide estimates for:

- the radiation exposure from the CT component of the study from the participating institutions;

and

- the total effective dose provided for the indicated study.

Generally, the sponsor should provide, as a summary in the IB, data to demonstrate that the clinical effective dose is the smallest radiation absorbed dose to allow, in the case of a diagnostic radiopharmaceutical, the greatest diagnostic performance or in the case of a therapeutic radiopharmaceutical, the desired therapeutic effect (i.e., the ALARA, "as low as reasonably achievable" principle).

3.3.3.3. Presentation of data

With respect to the presentation of data, the sponsor should present absorbed doses as a summary in the IB:

- in the ICRP format;

and

- in tabular summaries, where relevant, of the cumulative organ-absorbed radiation dose estimates from the radiopharmaceutical, and radionuclidic and radiochemical impurities that might be present in the final dosage form, expressed in mGy/MBq and mrad/mCi per unit activity injected.

The sponsor should also present the data using:

- the equivalent dose;

and

- effective dose per unit administered activity (mSv/MBq and mrem/mCi).

The following is a sample table for the presentation of final dose estimate data, where the sponsor should specify:

- the model and method used for calculation;
- human data used in the calculations, whereas supportive animal data would be included in the non-clinical section;
- supporting discussion or data or both, in terms of the potential for influence of pathophysiological changes induced by disease processes e.g., organs that are critical in metabolism or excretion of the radiopharmaceutical;
- when relevant, any additional information pertinent to the final dose estimates presented in the table, e.g., whether thyroid block was or was not used;
- for radiopharmaceuticals intended for pediatric uses, radiation dose estimates should be presented for the standard anthropomorphic phantoms as per the ICRP i.e., 15-year old, 10-year old, 5-year old, 1-year old, newborn;

and

- if the tabulated data is cited from the ICRP, this should be stated and referenced.

Organ	Absorbed dose per unit administered activity (mGy/MBq)	Absorbed dose per unit administered activity (rad/mCi)
-	-	-
-	-	-
Effective Dose (mSv/MBq)(rem/mCi)	-	-

3.3.4. Safety and efficacy studies

With respect to protocol considerations for safety and efficacy studies, radiopharmaceutical-specific submission considerations are set out below, where differences for diagnostic and therapeutic radiopharmaceuticals are indicated.

With respect to the design, conduct, and analysis of trials, the sponsor should state in the protocol the trial objectives, trial populations to be studied, and the trial endpoints (primary and secondary), which are all supported by an adequate statistical analysis plan. Specific factors to be considered include, but are not limited to

- for diagnostic radiopharmaceuticals:
    - diagnostic performance – diagnostic performance characterizes the sensitivity and specificity of the test under conditions studied or conditions of clinical use by comparing against a standard of truth. This is intended to support how the diagnostic radiopharmaceutical reflects the reality or truth as associated with a measurement or method that is regarded as the standard of truth or gold standard. When a standard of truth cannot be used or is unavailable, the sponsor should consult Health Canada in advance of the submission to address concerns regarding evidence of efficacy and clinical benefit.
    - technical performance – to establish and characterize the technical performance, the sponsor should provide data on concordance between multiple readers, and reproducibility of results. When applicable, the sponsor should provide comparison data with other diagnostic modalities;
    - clinical benefit – the sponsor should provide information on how the use of the diagnostic radiopharmaceutical impacts patient management decisions;
- for therapeutic radiopharmaceuticals:
    - non-inferiority or superiority trial designs;
    - how the drug fits into existing and established therapeutic cascades, which may involve concomitant use with other non-radiotherapeutic drugs;

- long-term safety effects when the drug is used for anticipated life-sustaining interventions, but not in the case where the drug is intended exclusively for symptom management, like pain palliation, in end-stage terminal illness;

and

- impact of the radiotherapeutic drug on subsequent patient management alternatives i.e., impact on options for subsequent lines of therapy, on possible repeat courses of therapy on advanced disease, on posssible relapse, etc.

The usual drug development cascade applies to clinical trial phases for radiopharmaceutical drugs. Considerations for each phase are outlined below.

Phase I studies are, generally, the first in-human exposure of the drug, that assesses pharmacokinetics and initial safety taking into account mass dose and biodistribution; and that assesses pharmacodynamics where the drug is intended to target specific receptors or metabolic processes. A difference between diagnostic and therapeutic radiopharmaceuticals is that

- for diagnostic radiopharmaceuticals: healthy volunteers would participate in Phase I CTAs, unless toxicity or radiation dose preclude exposure to healthy volunteers;

whereas

- for therapeutic radiopharmaceuticals: patients are studied in all CTA phases because toxicity and radiation dose preclude healthy volunteers from being exposed.

Phase II studies determine, generally, the dosage regimen characterization of the drug, to refine or verify the clinically relevant and useful mass dose and radiation activity dose range to be studied in later Phase III studies.

Phase II studies support pharmacokinetics and pharmacodynamics characterization, and allow the refining of timing, techniques, and processes

- for diagnostic radiopharmaceuticals: for imaging;

or

- for therapeutic radiopharmaceuticals: for fractionated therapy.

Phase II studies also show preliminary evidence of safety and efficacy in humans

- for diagnostic radiopharmaceuticals: to establish and assess diagnostic parameter performance, the sponsor should provide:
  - data from subjects with and without known disease;

  and
  - data that shows technical imaging quality.

Phase III studies are, generally, larger scale trials that establish efficacy and more thoroughly characterize the safety profile of the drug in a well-defined target

population under intended conditions and indications of actual clinical use. The design of Phase III studies reflects data and information from Phase II studies. Phase III studies are generally based on data from the drug formulation intended for marketing, where bridging studies should be provided in absence of data from the drug formulation intended for marketing. Multiple efficacy studies or multi-centered studies are often performed to increase the generalizability of the accrued data and results to the intended actual use and product performance profile.

Please see Section 3.3.5 - Biostatistics.

3.3.4.1. Pivotal trials

This section exists for NDS only, and is not applicable to CTA nor ANDS.

3.3.4.2. Non-pivotal trials

This section exists for NDS only, and is not applicable to CTA nor ANDS.

3.3.4.3. Other clinical studies

This section exists for NDS only, and is not applicable to CTA nor ANDS.

3.3.4.4. Other information

This section exists for NDS only, and is not applicable to CTA nor ANDS.

3.3.5. Biostatistics

The relevant principles outlined in ICH E9 and ICH E10 should be considered as needed in this section.

With respect to biostatistics for diagnostic radiopharmaceuticals, the sponsor should:

- provide a study protocol,
    - which gives details on the study objectives, study design, definition and establishment of the gold standard, diagnostic parameters to be assessed, and statistical methods;
    - which discusses measures to avoid or minimize bias;

    and
    - which is finalized before the start of the study, and where any changes to the protocol are introduced in a formal amendment to the protocol;
- specify in the protocol, with regard to diagnostic parameters, those that are critical to be evaluated e.g., sensitivity, specificity, and accuracy of the diagnostic radiopharmaceutical relative to the gold standard;
- ensure that blinded readers are used to interpret images, and provide information to support this in the protocol. If multiple readers are used, the

protocol should state whether the assessment of diagnostic parameters is based on each individual reader or on a majority read. If the latter, then the level of agreement amongst the different readers should be assessed, and the method for assessing the level of agreement should be described in the protocol. The handling of equivocal readings should be specifically addressed in the protocol, as should be the handling of missing or spurious data;

- provide a justification for the selected number of patients, ensuring that a sufficient number of both diseased and non-diseased patients are included in the study to allow sensitivity and specificity to be estimated with a high degree of precision;
- provide reference values in the protocol for comparing the diagnostic parameter estimates from the current study, which should be based on a well-planned and executed systematic review and meta-analysis of the relevant literature;

and

- provide details on the statistical approach that will be used to compare the diagnostic parameter estimates from the current study to the reference values derived from the literature specified in the protocol, including the success criteria for the study.

With respect to biostatistics for therapeutic radiopharmaceuticals, the sponsor should:

- provide the trial protocol,
    - which gives details on the trial's design, conduct, and statistical analysis;
    - which discusses measures to avoid or minimize bias, especially in open label trials with subjective endpoints;
    - which provides some assurance that the protocol, as proposed, results in sufficient data of high quality to allow a meaningful assessment of the efficacy and safety of the therapeutic radiopharmaceutical;
    - which is finalized before the start of the trial, and where there are justifications and documentation for any subsequent amendments to the protocol;
    - where the critical study design aspects are captured in the trial protocol e.g., the specific design for a given trial, the selected primary endpoint or endpoints if multiple primary endpoints are proposed, and the secondary endpoints;
    - which documents the role of the secondary endpoints in the overall interpretation of the trial results;

    and

    - which states whether the trial is designed to show superiority to the selected comparator, or is designed to show non-inferiority or equivalence, as per ICH guiding principles (see Section 6.4.2.1 – Reference 1);

and

- address additional considerations depending on the type of endpoints evaluated.
    - For instance, the use of tumour-based endpoints that are "time-to-event" in nature, such as progression-free survival, creates unique challenges; therefore, special attention should be paid to the collection, reporting, and analysis of such endpoints. Refer to FDA information on tumour-based endpoints (see Section 6.4.2.2 – United States Food and Drug Administration (FDA)).
    - In the case of therapeutic radiopharmaceuticals intended for pain palliation using subjective self-reported pain outcomes, the sponsor should provide evidence that the specific tool selected for assessing pain has been validated in a similar population to the population being evaluated in the current trial. The sponsor should also provide evidence that measures to minimize bias in the reporting of subjective pain outcomes have been put in place at the start of the trial. The sponsor should additionally:
        - provide a discussion of the clinical utility of the specific endpoint selected to demonstrate the effect of the therapeutic radiopharmaceutical on pain;
        - provide instructions on the use of concomitant analgesics permitted in the protocol;

        and
        - ensure that detailed information on the use of any additional pain medications is collected, recorded, and appropriately analyzed. The sponsor should then provide results from an assessment of the impact of additional pain medication on the primary and secondary outcome measures.

Finally, while the SAP should be developed along with the protocol prior to database lock, it does not need to be ready and finalized at the time of CTA filing.

4. SECTION NDS - SUBMISSION DATA SPECIFIC TO SCHEDULE C DRUGS FOR NEW DRUG SUBMISSIONS

See Section 2 - How to use this document for a description of how to jump forwards and backwards from the sub-Table of Contents for the NDS section.

The overview of SECTION NDS is:

4.1. QUALITY SUBMISSION DATA

Quality submission data is outlined in this Guidance document based on the Schedule C drug's emission characteristics (GERs, PERs, NGNPs) or how the Schedule C drug is manufactured (generators, kits).

4.1.1. Gamma-emitting radiopharmaceuticals (GERs)

A gamma-emitting radiopharmaceutical (GER) is a Schedule C drug that contains a gamma emitter, is pre-radiolabelled as a final drug product and is supplied in a ready-to-use dosage form. The GER is not further manipulated prior to administration of the product in patients, other than to measure the radioactive dose, pH, and perform radiochemical purity analysis, according to the PM.

Note on how to navigate 2 of the subsections that follow:

- If the GER contains a drug substance of chemical origin that is radiolabelled with a radionuclide, then both Section 4.1.1.2 - Drug substance synthesis and purification, and Section 4.1.1.3 - Radionuclide source and production apply;

and

- If the GER contains only the radionuclide or radiochemical, then only Section 4.1.1.3 - Radionuclide source and production applies e.g., when the GER is used in radiolabelling of a kit.

4.1.1.1. Source

With respect to source, the sponsor should:

- list the names and addresses of all facilities involved in the manufacture, packaging, labelling, and testing of the radionuclide, precursor or ligand, API or drug substance or both, and drug product.

4.1.1.2. Drug substance synthesis and purification

With respect to drug substance synthesis and purification, the sponsor should provide:

- a list of all raw materials, and a list of all starting materials, each of the materials with their C of A either from the vendor or generated in-house;
- details on synthesis, purification, and the structure elucidation process, including quality controls, specifications, and a flow chart identifying reaction yield;
- stability data under accelerated and real-time storage conditions in support of the claimed shelf-life;
- stability data for at least 3 consecutive commercial-scale batches;
- stability data generated at both upright and inverted orientations; or a rationale if data for only 1 orientation has been generated e.g, lyophilized pellet;

and

- the recommended shelf-life and its supporting study conditions and study duration.

Packaging should follow all applicable standards for the product type.

Labelling must follow the regulatory requirements referenced in Section 6.3 - Key legal references.

4.1.1.3. Radionuclide source and production

With respect to radionuclide source and production, the sponsor should provide:

- information on the radionuclide synthesis process, including details about the cyclotron, accelerator, reactor, or generator used; when applicable, a DMF should be submitted or cross-referenced or both;
- detailed information on the target, including target body; information on other raw materials should be submitted if not included in the DMF;
- C of A for the target material either from the vendor or generated in-house;
- specifications of the radionuclide;
- analysis of radionuclidic, radiochemical, and chemical purity and impurity;
- analysis of target breakthrough in the final radionuclide (i.e., desired product) such as Mo-100 in Tc-99m made directly via cyclotron or accelerator;

and

- if the radionuclide is used in manufacturing to radiolabel ligands, then data should be generated for kits containing anionic, cationic, and neutral ligands if the radionuclide is intended to radiolabel kits or other ligands.

4.1.1.4. Development pharmaceutics

With respect to development pharmaceutics, the sponsor should provide any development work that was carried out, including formulation, batch size and strength, and its method of manufacture, to determine that the following are satisfactory for the intended use of the drug product:

- the radionuclide, API or drug substance, or radiopharmaceutical;

and

- any other ligand or precursor in the production of the final drug product.

4.1.1.5. Formulation and drug product manufacturing

With respect to formulation and drug product manufacturing, the sponsor should provide:

- a table identifying all ingredients and their roles in the formulation;
- detailed information on the manufacturing process, including radiolabelling, purification, vial filling, vial stoppering, and packaging;
- batch analyses data, and batch production records with release specifications for at least 3 commercial-scale batches of the final product; additionally, the sponsor should indicate which tests are done prospectively, and which tests are done retrospectively;
- SOPs for all analytical procedures with their validation study data;

and

- shipping validation data covering the furthest distance simulating the real-life commercial supply; or if not possible, a statement that the end user is responsible for performing stability indicating tests i.e., the percentage of radiochemical purity, the pH, and the appearance of the final drug product as set out in the PM.

4.1.1.6. Stability and packaging

With respect to product stability and compatibility with packaging materials which are in direct contact with the drug product (e.g., vials, stoppers), the sponsor should provide stability data:

- for 3 consecutive commercial-scale batches using accelerated and real-time storage conditions;
- generated at both upright and inverted orientations;

and

- for at least 3 time points to support the recommended shelf-life that reflects study conditions and duration.

Packaging should follow all applicable standards for the product type.

Labelling must follow the regulatory requirements referenced in Section 6.3 - Key legal references.

4.1.1.7. Pharmaceutical comparability and equivalency

This section exists for ANDS only, and is not applicable to CTA nor NDS.

4.1.2. Positron-emitting radiopharmaceuticals (PERs)

A positron-emitting radiopharmaceutical (PER) is a Schedule C drug that contains a cyclotron-produced or accelerator-produced positron emitter, such as Carbon-11 (C-11), Nitrogen-13 (N-13), Oxygen-15 (O-15), or Fluorine-18 (F-18). One of the most common PERs is F-18 labelled Fluorodeoxyglucose (FDG).

Note:

- PERs that are manufactured using radionuclide generators are not addressed in Section 4.1.2 - Positron-emitting radiopharmaceuticals (PERs), but are addressed in Section 4.1.4 - Generators.

4.1.2.1. Source

With respect to source, the sponsor should:

- list the names and addresses of all facilities involved in the manufacture, packaging, labelling, and testing of the radionuclide, precursor or ligand, API or drug substance or both, and drug product.

4.1.2.2. Precursor, ligand, or drug substance source and synthesis

With respect to the source and synthesis of the precursor or ligand, the sponsor should indicate if the precursor or ligand is available commercially, synthesized in-house, or synthesized by a contract manufacturer.

If the precursor or ligand is a commercial product (e.g., mannose triflate), the sponsor should provide the name and C of A from the vendor, including storage conditions and expiry date.

Whether the precursor or ligand is synthesized by the sponsor or a contract manufacturer, the sponsor should provide:

- a list of all raw materials, and a list of all starting materials each with their C of A either from the vendor or generated in-house;
- details on synthesis, purification, and structure elucidation process of the precursor or ligand, including a flow chart with reaction yield, quality control, and specifications;
- stability data under accelerated and real-time storage conditions in support of the claimed shelf-life;
- stability data for at least 3 consecutive commercial-scale batches;
- stability data generated at both upright and inverted orientations; or a rationale if data for only 1 orientation has been generated;

and

- the recommended shelf-life and its supporting study conditions and study duration.

Packaging should follow all applicable standards for the product type.

Labelling must follow the regulatory requirements referenced in Section 6.3 - Key legal references.

4.1.2.3. Radionuclide source and production

With respect to radionuclide source and production, the sponsor should provide:

- information about the cyclotron used e.g., type, size or capacity, target size, target body type, beam current and irradiation time;
- detailed information on the target e.g., enrichment level, vendor name with the C of A;
- information on enrichment level and procedure with respect to whether the target is reused or recycled;
- information about the radionuclide production or synthesis process; when applicable, a DMF should be submitted or cross-referenced or both;
- information about other raw materials used for processing or purification beyond the scope of the DMF;
- specifications of the radionuclide, including acceptance limits of other radionuclidic impurities;

and

- in the case where the radionuclide is imported, information about the shipping process and further manufacturing, including details of the processing on receipt at the site prior to use in radiosynthesis.

4.1.2.4. Development pharmaceutics

With respect to development pharmaceutics, the sponsor should provide any development work that was carried out, including formulation, batch size and strength, and method of manufacture, to determine that the following are satisfactory for the intended use of the drug product:

- the radionuclide, API or drug substance, or radiopharmaceutical;

and

- any other ligand or precursor in the production of the final drug product.

4.1.2.5. Formulation and drug product manufacturing

With respect to formulation and drug product manufacturing the sponsor should provide:

- a quantitative formulation table for a batch and unit vial, including the radioactivity range (in MBq or mCi), identifying all ingredients and their roles in the formulation;
- details of the manufacturing process with respect to the Automated Synthesis Unit or Semi-Automated Synthesis Unit or manual radiolabelling; the deprotection and purification processes including radiochemical yield at the end of synthesis;
- details of the vial filling, stoppering, labelling, and packaging;
- for ASU or S/ASU, the type of cartridge or manifold used, and its vendor information;

- batch analyses data and batch production records with release specifications for at least 3 commercial-scale batches of the final product; additionally, the sponsor should indicate which tests are done prospectively, and which tests are done retrospectively;
- SOPs for all analytical procedures with their validation study data;

and

- shipping validation data covering the furthest distance simulating the real-life commercial supply; or if not possible, a statement that the end user is responsible for performing stability indicating tests i.e., the percentage of radiochemical purity, the pH, and the appearance of the final drug product as set out in the PM.

4.1.2.6. Stability and packaging

With respect to product stability and compatibility with packaging materials which are in direct contact with the drug product (e.g., vials, stoppers), the sponsor should provide stability data:

- for 3 consecutive commercial-scale batches using accelerated and real-time storage conditions;
- generated at both upright and inverted orientations; or a rationale if data for only 1 orientation has been generated;

and

- for at least 3 time points to support the recommended shelf-life that reflects study conditions and duration.

Packaging should follow all applicable standards for the product type.

Labelling must follow the regulatory requirements referenced in Section 6.3 - Key legal references.

4.1.2.7. Pharmaceutical comparability and equivalency

This section exists for ANDS only, and is not applicable to CTA nor NDS.

4.1.3. Non-GERs non-PERs radiopharmaceuticals (NGNP)

A non-GERs non-PERs radiopharmaceutical (NGNP) is a Schedule C drug produced by a linear accelerator or nuclear reactor. NGNPs include alpha emitters and negatron emitters (beta minus). NGNPs include, but are not limited to, radionuclides such as Astatine-211 (As-211), Iodine-131 (I-131), Lutetium-177 (Lu-177), Radium-223 (Ra-223), Rhenium-188 (Re-188), Samarium-153 (Sm-153), Thorium-227 (Th-227), and Yttrium-90 (Y-90).

Note on how to navigate 2 of the subsections that follow:

- If the NGNP contains a drug substance of chemical origin that is radiolabelled with a radionuclide, then both Section 4.1.3.2 - Drug substance synthesis and purification, and Section 4.1.3.3 - Radionuclide source and production apply;

and

- If the NGNP contains only the radionuclide or radiochemical, then only Section 4.1.3.3 - Radionuclide source and production applies.

4.1.3.1. Source

With respect to source, the sponsor should:

- list the names and addresses of all facilities involved in the manufacture, packaging, labelling, and testing of the radionuclide, precursor or ligand, API or drug substance or both, and drug product.

4.1.3.2. Drug substance synthesis and purification

With respect to drug substance synthesis and purification, the sponsor should provide:

- a list of all raw materials, and a list of all starting materials each with their C of A either from the vendor or generated in-house;
- details on synthesis, purification, and the structure elucidation process, including quality controls, specifications, and a flow chart identifying reaction yield;
- stability data under accelerated and real-time storage conditions in support of the claimed shelf-life;
- stability data for at least 3 consecutive commercial-scale batches;
- stability data generated at both upright and inverted orientations; or a rationale if data for only 1 orientation has been generated;

and

- the recommended shelf-life and its supporting study conditions and study duration.

Packaging should follow all applicable standards for the product type.

Labelling must follow the regulatory requirements referenced in Section 6.3 - Key legal references.

4.1.3.3. Radionuclide source and production

With respect to radionuclide source and production, the sponsor should provide:

- information on the radionuclide synthesis process, including details about the cyclotron, accelerator, reactor, or generator used; when applicable, a DMF should be submitted or cross-referenced or both;
- detailed information on the target, including target body; information on other raw materials should be submitted if not included in the DMF;

- C of A for the target material from either the vendor or generated in-house;
- specifications of the radionuclide;
- analysis of radionuclidic, radiochemical, and chemical purity and impurity;
- analysis of target breakthrough in the final radionuclide (i.e., desired product) such as Te-131 in I-131, or W-188 in Re-188, or Re-185 in Re-186, produced by a linear accelerator;

and

- radiolabelling data if the radionuclide is intended to radiolabel kits or other ligands.

4.1.3.4. Development pharmaceutics

With respect to development pharmaceutics, the sponsor should provide any development work that was carried out, including formulation, batch size and strength, and its method of manufacture, to determine that the following are satisfactory for the intended use of the drug product:

- the radionuclide, API or drug substance, or radiopharmaceutical;

and

- any other ligand or precursor in the production of the final drug product.

4.1.3.5. Formulation and drug product manufacturing

With respect to formulation and drug product manufacturing, the sponsor should provide:

- a quantitative formulation table for a batch and unit vial, including the radioactivity range (in MBq or mCi), identifying all ingredients and their roles in the formulation;
- detailed information on the manufacturing process, including radiolabelling, purification, vial filling, vial stoppering, and packaging;
- batch analyses data and batch production records with release specifications for at least 3 commercial-scale batches of the final product; additionally, the sponsor should indicate which tests are done prospectively, and which tests are done retrospectively;
- SOPs for all analytical procedures with their validation study data;

and

- shipping validation data covering the furthest distance simulating the real-life commercial supply; or if not possible, a statement that the end user is responsible for performing stability indicating tests i.e., the percentage of radiochemical purity, the pH, and the appearance of the final drug product as set out in the PM.

4.1.3.6. Stability and packaging

With respect to product stability and compatibility with packaging materials which are in direct contact with the drug product (e.g., vials, stoppers), the sponsor should provide stability data:

- for 3 consecutive commercial-scale batches using accelerated and real-time storage conditions;
- generated at both upright and inverted orientations;

and

- for at least 3 time points to support the recommended shelf-life that reflects study conditions and duration.

Packaging should follow all applicable standards for the product type.

Labelling must follow the regulatory requirements referenced in Section 6.3 - Key legal references.

4.1.3.7. Pharmaceutical comparability and equivalency

This section exists for ANDS only, and is not applicable to CTA nor NDS.

4.1.4. Generators

A generator is defined in Part C, Division 3 of the *Food and Drug Regulations* (C.03.001).

A generator typically contains a column with a large amount of a radionuclide (i.e., parent radionuclide) that decays down to a second radionuclide of shorter half-life (i.e., daughter radionuclide). The daughter radionuclide is separated from the parent by the process of elution, which gives a continuing supply of relatively short-lived radionuclides.

4.1.4.1. Source

With respect to source, the sponsor should:

- list the names and addresses of all facilities involved in the manufacture, packaging, labelling, and testing of the radionuclide, precursor or ligand, API or drug substance or both, and drug product.

4.1.4.2. Parent radionuclide and processing

With respect to the parent radionuclide and its processing, the sponsor should provide:

- general information about the production, properties, and quality control of the parent radionuclide e.g., C of A for radionuclidic,

radiochemical, and chemical purity and impurities, specific activity, activity concentration, pH, appearance, etc.;

- detailed information about the accelerator or reactor used. Alternatively, the sponsor should cross-reference a DMF;

and

- detailed information about the target or target body. Additionally, the sponsor should provide detailed information about other raw materials when not included in the DMF.

4.1.4.3. Development pharmaceutics

With respect to development pharmaceutics, the sponsor should provide any development work that was carried out to determine that the following are satisfactory:

- the parent radionuclide e.g., its amount, column type and length, adsorbent material and its amount, other materials used in the production of the generator including its formulation and batch size;

and

- the parent radionuclide's method of manufacture.

4.1.4.4. Formulation and generator manufacturing process

With respect to formulation and generator manufacturing process, the sponsor should provide:

- the names and addresses of all facilities involved in the production and processing of the parent radionuclide and the generator;
- the formulation and production methodology of the generator, including total radioactivity of the generator, type and source of adsorbent, tubing, sterile filter, collection vial etc.;
- in the case where the eluate is for direct administration, details about dose preparation i.e., volume, specific activity, total radioactivity, radioactive concentration, and other appropriate data;
- specifications for the final product (i.e., the eluate) which should at least include appearance, radionuclidic purity, radiochemical purity, percentage of parent radionuclide breakthrough or radioactive amount present (in MBq or mCi) and the amount of adsorbent material present, pH, and osmolality;
- confirmation of which quality control test parameters are done at release, and which are done retrospectively;
- batch analysis data, including data for tests done retrospectively, for at least 3 consecutive batches;

and

- in the case where the daughter radionuclide radiolabels kits or other ligands, radiolabelling data for kits containing anionic, cationic, and neutral ligands. If the radionuclide is only to be used to radiolabel a

specific kit or ligand, then the sponsor should provide radiolabelling data for that particular kit or ligand.

4.1.4.5. Stability and packaging

With respect to stability and packaging, the sponsor should provide, for 3 consecutive commercial-scale batches:

- data to support generator stability for the column, including for parent radionuclide and column adsorbent breakthrough throughout the shelf-life of the generator, and its eluate specifications for percentage of radiochemical purity, percentage of radionuclidic purity, pH, and appearance;
- data to support the expiry date of the eluate at post-elution, including storage conditions;
- data to support stability associated with compatibility of the vial content with the container closure i.e., a study performed by storing at the upright and inverted orientations for up to the proposed expiry period;

and

- information that shows that packaging is according to generator type and size with required shielding as specified by the CNSC.

Packaging should follow all applicable standards for the product type.

Labelling must follow the regulatory requirements referenced in Section 6.3 - Key legal references.

4.1.4.6. Pharmaceutical comparability and equivalency

This section exists for ANDS only, and is not applicable to CTA nor NDS.

4.1.5. Kits

A kit is defined in Part C, Division 3 of the *Food and Drug Regulations* (C.03.205).

A kit is a Schedule C drug that is used in the preparation of a radiopharmaceutical.

4.1.5.1. Source

With respect to source, the sponsor should:

- list the names and addresses of all facilities involved in the manufacture, packaging, labelling, and testing of the API or drug substance, and drug product.

4.1.5.2. Drug substance synthesis and purification

With respect to drug substance synthesis and purification, the sponsor should provide:

- a list of all raw materials, and a list of all starting materials each with their C of A either from the vendor or generated in-house;
- details on synthesis, purification, and the structure elucidation process, including quality controls, specifications, and a flow chart identifying reaction yield;
- stability data under accelerated and real-time storage conditions;
- the DMF obtained from the supplier, in the case where the drug substance is manufactured by a contract manufacturer;

and

- shipping validation data in the case where the product is shipped from off-site, including specific shipping information for thermolabile or photosensitive products.

4.1.5.3. Development pharmaceutics

With respect to development pharmaceutics, the sponsor should provide any development work that was carried out to determine that the following are satisfactory:

- the drug substance, excipients, and radionuclide(s) used in reconstitution;
- their amounts;

and

- any other materials used in the preparation of the final drug product, including its formulation, batch size and strength, and its method of manufacture.

4.1.5.4. Formulation and drug product manufacturing

With respect to formulation and drug product manufacturing, the sponsor should provide:

- a table identifying all ingredients and their roles in formulation;
- detailed information on the manufacturing process, including purification, vial filling, vial stoppering, lyophilization, and packaging;
- batch analyses data, and batch production records that include release specifications for the radiolabelling method and analysis of percentage of radiochemical purity and impurities for the following 3 situations:
    - using a radionuclide from a source approved in Canada or an eluate from a generator approved in Canada;
    - obtaining Tc-99m or other gamma-emitting radionuclides from a generator. In this situation, the sponsor should additionally provide data that demonstrates that conditions, such as when the eluate is more than 2 hours old and from a

generator not eluted for more than 72 hours, do not affect the desired radiolabelling yield, nor the radiochemical purity and impurity profiles;

or

- obtaining radionuclides other than Tc-99m from a generator (e.g., Re-186). In this situation, the sponsor should additionally provide data that demonstrates that conditions do not affect the desired radiolabelling yield, nor the radiochemical purity and impurity profiles e.g., placing limits on the expiry of the eluate related to when the generator was last eluted, or when the generator is not eluted in the specified time;
    - If the second situation listed above is not met, the sponsor should state in the PM the generator-specific conditions with the eluate-specific conditions, such as the eluate is not over 2 hours old from a generator eluted within the last 24 hours;

- SOPs for all analytical procedures with associated validation study data;

and

- shipping validation data for the kit covering the furthest distance simulating real-life commercial supply.

4.1.5.5. Stability and packaging

With respect to stability and packaging, the sponsor should provide:

- stability data for 3 consecutive commercial-scale batches, for both real-time and accelerated storage conditions for the drug product (cold kit);
- real-time stability data for 3 consecutive commercial-scale batches for the final radiolabelled drug product;
- study data generated at both upright and inverted orientations for the cold kit and the final radiolabelled drug product;

and

- data for at least 3 time points to support the recommended shelf-life that reflects study conditions and duration, for both:
    - the drug product (cold kit);

    and
    - the final radiolabelled drug product.

Packaging should follow all applicable standards for the product type.

Labelling must follow the regulatory requirements referenced in Section 6.3 - Key legal references.

4.1.5.6. Pharmaceutical comparability and equivalency

This section exists for ANDS only, and is not applicable to CTA nor NDS.

4.2. NON-CLINICAL SUBMISSION DATA

This introduction provides sponsors with key general information that underlies the specific non-clinical submission data requested in the non-clinical subsections below.

Non-clinical submission data is outlined in this Guidance document for all Schedule C drugs, regardless of how the drug is used (e.g., diagnostic or therapeutic). When there are differences in submission data for diagnostic and therapeutic radiopharmaceuticals, they are set out.

- Diagnostic radiopharmaceuticals are used to diagnose, monitor, or determine the stage of a disease or condition. Clinical treatment platforms are structured for these specific clinical indications, therefore many standardized principles and guidelines for clinical study design, conduct, data processing and analysis apply to diagnostic radiopharmaceuticals.
- Therapeutic radiopharmaceuticals are used to treat or manage a disease or condition. The drug development cascade and clinical platforms and expectations for other therapeutic drug products (i.e., pharmaceuticals or biologics) typically apply to therapeutic radiopharmaceuticals.

Goals: The primary goals of a non-clinical safety evaluation for Schedule C drugs are the same as for all drugs, and should include:

- to identify safe dose ranges, and subsequent dose exposure in humans;
- to identify potential target organs for toxicity, and for the study of whether such toxicity is reversible;
- to identify safety parameters where clinical monitoring may be needed;

and

- to assess biological, physical, and effective half-life considerations and critical dose organs that impact the radiation dosimetry estimates and evaluation.

Studies: Non-clinical, single-dose, toxicity studies should be completed before the first introduction of the drug into humans. These studies should examine at least a 100X greater dose than the maximal anticipated human mass dose. Most radiopharmaceuticals can be administered at a low mass dose of the ligand for an intended single dose, or a very limited number of repeated single doses. When the mass dose is administered at the low end of a dose-response curve, dose-related pharmacologic effects, or adverse events associated with a pharmacologic effect, are less likely to occur. Typically, all non-clinical studies can be conducted with non-radiolabelled material, except for biodistribution studies.

Biological activity: Biological activity jointly with tissue specificity should be taken into account in standard toxicity testing designs, depending on the choice of animal species or when the ligand is a biologic (e.g., monoclonal antibody). Non-clinical studies should use relevant species, when applicable, where the test material is pharmacologically active as a result of the expression of the receptor (e.g., as with monoclonal antibodies). Animal species that do not express the desired epitope may be relevant if comparable tissue cross-reactivity to humans is demonstrated.

Product formulation: The product formulation used in non-clinical studies and safety margin estimations should ideally be the same formulation intended for use in clinical trials and the marketplace. If the product formulation changes during product development, a rationale, and potentially bridging data, should be generated to substantiate the data linkages with the different formulations. Bridging data should be used when formulation changes could result in altered pharmacokinetics or pharmacodynamics (hence potentially altered radiation dosimetry), or overall safety considerations. Bridging data should help facilitate comparisons between data sets and formulations, especially if there have been changes between the species or animals used in non-clinical or clinical studies, or both.

Toxicology: Drug product components should be considered in the toxicological assessment e.g., non-medicinal ingredients, excipients, impurities, etc. Components may need specific and detailed testing individually if toxicological data is generally lacking. Individual component studies are not usually required if testing is performed on combined components and results are unremarkable. When undertaken, genotoxicity of the non-radioactive component should be conducted separately so as to distinguish it from that of the radionuclide. When the mass dose administered is at the low end of the dose-response curve (e.g., micro-dose), certain elements of the toxicological assessment (e.g., genotoxicity and mutagenicity) may not be required if supported by a rationale provided by the sponsor.

General: The non-clinical study component of development should be based on sound scientific and clinical principles and should be linked with the proposed product's unique properties (taking into account the ligand and radionuclide) and intended clinical use(s). The number and types of non-clinical studies depend on stage of development and information already known about the constituents, including the pharmacologic profile, intended use, and target patient population.

Specifics - additional information for diagnostic radiopharmaceuticals:

- Long-term repeat-dose toxicity non-clinical studies are not typically required for diagnostic radiopharmaceuticals due to their typical characteristics and patterns of intended use. Long effective half life is an example of an exception.
- Studies of long-term carcinogenicity and developmental and reproductive toxicity are not typically undertaken unless there are indicators from rodent and non-rodent short-term toxicity studies e.g., embryonic and fetal toxicities that increase the uncertainty of reproductive and developmental risk.

Specifics - additional information for therapeutic radiopharmaceuticals is based on the intended nature of these products as a therapeutic intervention in a treatment capacity, thus delivering a therapeutic absorbed radiation dose:

- In instances of fractionated dosing, repeated dose exposure should be typically done at specific intervals for a targeted cumulative dose. When repeat divided dosing involves a radiopharmaceutical that consists of a biologic ligand, the immunogenic potential should be considered, and the immunogenicity profile should be examined and characterized.
- The effect on radiation dosimetry of variations in biodistribution results or product design (e.g., specific receptor or organ targets) should be investigated in order to help characterize the safety profile of the drug, because change in radiation dosimetry may occur in the presence of diseases in organs related to metabolism or excretion.
- The effect on radiation dosimetry of variations in receptor mass or antigen burden should be investigated in order to facilitate optimal dose range or dose-characterizing studies in patients.

4.2.1. Pharmacology

4.2.1.1. Primary pharmacodynamics

With respect to primary pharmacodynamics, the sponsor should provide:

- studies that characterize mode of action with respect to its desired effect.

Additional information for diagnostic radiopharmaceuticals: These types of studies should reflect groupings of intended diagnostic use, and may relate to anatomic structure delineation; or functional, physiological, or biological evaluation.

Additional information for therapeutic radiopharmaceuticals: These types of studies should reflect groupings of intended therapeutic use for conditions or disease states.

4.2.1.2. Secondary pharmacodynamics

With respect to secondary pharmacodynamics, the sponsor should provide:

- studies that address one or both modes of action, or effects of the product not related to the product's diagnostic capabilities, or therapeutic effect. These considerations may be pertinent to safety.

4.2.1.3. Safety pharmacology

With respect to safety pharmacology, the sponsor should provide:

- safety pharmacology studies that investigate the potential effects of the test material on vital functions in core organ systems, such as cardiovascular (including QT prolongation studies), respiratory, and central nervous systems.

Additional information for therapeutic radiopharmaceuticals:

- prior to first in-human exposure, safety pharmacology studies should also include a focus on major organs or organ systems that the therapeutic radiopharmaceutical is intended to target;

and

- other safety studies that investigate the effect of the test material on other organ systems, based on the pharmacological activity profile of the ligand associated with the product. These organ systems include, for example, renal/urinary, autonomic nervous, gastro-intestinal, muscle, immune, endocrine systems.

4.2.2. Pharmacokinetics

This introduction provides sponsors with key general information that underlies all specific non-clinical submission data requested in the subsections that follow.

Pharmacokinetic studies should use, when possible:

- preparations representative of intended toxicity testing and clinical use;

and

- the route of administration in anticipated clinical studies.

When using radiolabelled ligands, it should be shown that radiolabelled material maintains biological properties and receptor affinity equivalent to that of the un-radiolabelled material.

- For the therapeutic radioactive dose, this can be particularly relevant, given the larger activity amounts that are administered.
- For diagnostic agents that have a different chemical structure than their precursor, the unlabelled ligand may not be relevant for study e.g., labelled compounds where the structural contribution from the radionuclide is integral to biological properties.

4.2.2.1. Analytical methods and validation

With respect to analytical methods and validation, the sponsor should provide:

- evidence that methods are validated according to standard procedures for quantitative analytical assay performance.

4.2.2.2. Absorption, distribution, metabolism, excretion

With respect to absorption, distribution, metabolism, and excretion, the sponsor should provide:

- a characterization of the disposition (distribution and elimination) of the radiolabelled compound, including the nuclear physics, mode of decay etc., of the radionuclide.

Note:

- Characterization is requested because biological, physical, and effective half-lives are incorporated into radiation dosimetry estimates and evaluations.
- The nuclear physics, mode of decay etc., of the radionuclide should be used in non-clinical-to-clinical exposure estimations for absorbed radiation doses (i.e., radiation dosimetry) prior to characterization in humans. Such estimates of absorbed dose establish the dosing platform for both first clinical exposures and further clinical trials that assess safety and efficacy in patients.

4.2.3. Radiation dosimetry

This introduction provides sponsors with key general information that underlies the radiation dosimetry specific submission data requested in the subsections below.

With respect to radiation absorbed dose estimates, the sponsor should provide:

- the actual biodistribution and radiation absorbed dose resulting from the recommended amount of administered radioactivity. This information is unique to each radiopharmaceutical product;
- sufficient data from animal studies to be able to refine dose selection when the product is later administered to a patient, so that the radiation absorbed dose estimates can be characterized and confirmed from actual human data;

and

- the rationalization for dose selection and the verification of nominal choice for the activity to be administered, with the safety/benefit profile of the product under conditions of clinical use.

For submission data in the next stage of development, continue onwards to the NDS Clinical section, Section 4.3, in this Guidance.

4.2.3.1. Biodistribution, corroborating data, assumptions, and models

With respect to biodistribution and corroborating data for radiation absorbed dose estimates, the sponsor should provide:

- all sources of data from animal biodistribution studies used to calculate radiation absorbed dose estimates;
- a description of models used to calculate radiation absorbed dose estimates;

and

- an analysis of all assumptions used in any dose calculation.

With respect to radiation absorbed dose estimates in animal models, the sponsor should provide:

- a summary of dose estimates;
- a presentation of corroborating data (parameters, assumptions, models, etc.) used to calculate the dose estimates;
- dose estimates calculated from biodistribution data;

and

- estimates of the equivalent dose or the effective dose or both, per unit administered activity (mSv/MBq and mrem/mCi) for each phantom.

The sponsor should provide the characterization of radiation dosimetry:

- a summary of dose estimates;

and

- a presentation of corroborating data (parameters, assumptions, models, etc.) used to calculate the final dose estimates.

Presentation of the raw data used to derive the parameters should be available upon request.

4.2.3.2. Summary of radiation dose estimates

With respect to radiation absorbed dose estimates, the sponsor should provide overall radiation dose estimates that include:

- the radionuclide used in the formulation of the drug (i.e., the principal radionuclide);

and

- any radiochemical or radionucludic impurities that may contribute substantially to the total effective dose.

These inclusions can help characterize the absorbed dose that may be impacted by such impurities, and is a means to help account for contributions to the total radiation burden e.g., effective dose.

4.2.3.3. Presentation of data

This section exists for Clinical CTA and Clinical NDS only, and is not applicable to Non-clinical NDS.

4.2.4. Toxicology

This introduction provides sponsors with key general information that underlies the toxicology specific submission data requested in the subsections below.

Most diagnostic radiopharmaceuticals can be administered at a low mass dose of the ligand for a single dose, or a very limited number of repeated single doses. When the mass dose is administered at the low end of a dose-response curve (e.g., micro-dose administration), dose-related pharmacologic effects or adverse events associated with a pharmacologic effect are less likely to occur. Multiple dose levels greater than those for clinical use are used in toxicology studies.

Assessment may include a non-radioactive component or the radiolabelled compound or both. Therefore the design of toxicology studies should take into account the radiopharmaceutical's biological and physical half-lives. The studies can be done using the ligand, or the radiopharmaceutical after it is has decayed. In the case of therapeutic radiopharmaceuticals, the radiolabelled compound is preferred in order to assess the late radiation toxicity.

A distinction is also made between ligands of biological and chemical origins. Specific guidance for biologics should also be taken into account where needed. Biological ligands are usually large molecules i.e., peptides or proteins. Many are species-specific and engineered for human use, thus may cause formation of anti-drug antibodies or neutralizing antibodies that could interfere with the conduct of animal studies. In these cases, use of a homologous protein may be considered. Immunogenicity is a toxicological and safety concern when a biologic is the ligand and should be investigated. Products with a biologic as the ligand typically require consideration on a case-by-case basis. Standard toxicity testing protocols may not always be appropriate for such biotechnology products, and instead the parameters may utilize studies that incorporate alternate or specialized test parameters, such as transgenic or animal versions of human protein and disease models.

With respect to single dose or repeat dose studies, the sponsor should provide:

- data from preferably 2 relevant mammalian species, rodents and non-rodents. Alternatively, when not possible in the case of biologic ligands, the sponsor should provide data from 1 relevant mammalian species;
- data that demonstrates an adequate number of animals were used for valid statistical analysis. When not possible in the case of non-human primates, the sponsor should provide a justification for restricted sample size;
- evidence from evaluations done after the exposure that assess any delay of toxicity and monitor for any recovery;
- data that demonstrates that both sexes are tested. Alternatively, the sponsor should provide a justification for why only 1 sex is tested;
- data that demonstrates sufficient multiples of dose levels for the intended clinical maximal mass dose;
- data that demonstrates the level of exposure of test material on test animals, relative to clinical exposure to humans;

and

- immunogenicity data in the case of biologic ligands for toxicology safety reasons.

4.2.4.1. Single-dose acute toxicity studies

With respect to single-dose studies and acute toxicity, the sponsor should provide a summary of each study including:

- the species, number, sex, weights, and strains of animals;
- information on dosage, formulation, routes of administration, and duration of treatment;
- methodology;
- parameters evaluated in clinical observations (e.g., vital signs, local tolerance etc.);
- hematology, clinical chemistry, and histopathology;
- any other pertinent information;
- further to study protocol, the above information presented separately for animals sacrificed during and at the end of the 14-day observation period e.g., extended single-dose studies to assess for maximum effect and recovery;
- endpoints (e.g., non-lethal dose, no toxic effect level) with their ratios to the proposed maximal human mass dose;
- data that demonstrates the NOAEL, by using multiple dose levels of 100X or greater than the mass dose intended for clinical use;

and

- study conclusions.

Sponsors should follow guidelines on GLPs set out in Section 6.4.1.1 – World Health Organisation (WHO).

4.2.4.2. Repeat-dose studies

With respect to repeat-dose studies evaluating multiple-dose toxicity, the sponsor should provide a summary of each study including:

- the species, number, sex, weights, and strains of animals;
- information on dosage, formulation, routes of administration, and duration of treatment;
- methodology;
- parameters evaluated in clinical observations (e.g., vital signs, local tolerance etc.);
- hematology, clinical chemistry, and histopathology;
- any other pertinent information;
- results, such as the nature and severity of target organ toxicity, dose exposure-response relationships, or differences between species, gender, etc.;

- evidence from evaluations done after the recovery period, that assess reversibility of any toxicological effects and the potential for delayed toxicity;
- data that demonstrates the NOAEL after using multiple dose levels greater than the mass dose intended for clinical use;
- further to study protocol when relevant, estimates of the maximal tolerated doses for specific toxic effects and their relationship to the proposed maximum human dose;

and

- study conclusions.

Sponsors should follow guidelines on GLPs set out in Section 6.4.1.1 – World Health Organisation (WHO).

4.2.4.3. Genotoxicity and mutagenicity

With respect to genotoxicity and mutagenicity, the sponsor should provide 2 sets of data for separately conducted genotoxicity studies addressing:

- the non-radioactive component;

and

- the radionuclide;

in order to distinguish the effect of the non-radioactive component from that of the radionuclide.

When the mass dose administered is at the low end of the dose-response curve (e.g., micro-dose) or when the ligand is a biologic, certain elements of the toxicological assessment may not be required when supported by a rationale provided by the sponsor.

4.2.4.4. Carcinogenicity

Unless specifically requested by Health Canada, the sponsor can omit long-term animal studies that evaluate carcinogenic potential if supported by a rationale. Depending on intended product use, alternate methodologies for determining carcinogenic potential may be appropriate.

Product-specific assessment of carcinogenic or mutagenic potential may still be necessary for diagnostic and therapeutic radiopharmaceuticals, depending upon clinical dosing, patient population or biological activity of the product or both.

- In particular for therapeutic radiopharmaceuticals, the sponsor should address the risk of mutagenic and carcinogenic effects because there is an increased exposure to ionizing radiation. Literature sources may be acceptable.

4.2.4.5. Reproductive and developmental toxicities

With respect to reproductive and developmental toxicities,

- in the case of diagnostic radiopharmaceuticals: the sponsor can generally omit reproductive toxicity non-clinical studies because of their typical characteristics and patterns of intended use.
    - However, in exceptional cases, such as for long effective half-life considerations, the sponsor should provide data from short-term toxicity studies in rodents and non-rodents where limited embryonic and fetal toxicities are a related component. If these studies in exceptional cases are not conducted, the sponsor should include a rationale.
- in the case of therapeutic radiopharmaceuticals: the sponsor should provide data from reproductive and developmental toxicity studies that evaluate the risk of reproductive and developmental effects, because there is an increased radiation exposure compared with diagnostic radiopharmaceuticals.

4.2.4.6. Other information

In addition to the submission data requested above, the sponsor may provide other information to support their toxicity studies e.g.,

- data from additional studies that assess the toxicological profile of the test material e.g., ligand-receptor binding studies, cross-reactivity studies, and a QT prolongation study;
- data from original articles published in peer-reviewed journals and sourced from multiple labs, research centres, or academic centres i.e., published data that is valid and supported by the scientific community. The data should be supportive of submissions (e.g., pharmacology, pharmacokinetics, toxicology, radiation dosimetry estimates etc.), and should represent a raw material of interest (i.e., associated with the drug substance or ligand), since such data is not usually generated for the specific formulation under development (i.e., the drug product);

or

- data with the specific drug development process taken into account, as differences in manufacturing and production may have an impact on quality.

4.3. CLINICAL SUBMISSION DATA

This introduction provides sponsors with key general information that underlies all specific clinical submission data requested in the clinical subsections below.

Clinical submission data is outlined in this Guidance document based on the clinical use of the Schedule C drug.

There are 2 types of Schedule C drugs with respect to clinical submission data: diagnostics and therapeutics.

- Diagnostic radiopharmaceuticals are used to diagnose, monitor, or determine the stage of a disease or condition. Clinical treatment platforms are structured for these specific clinical indications, therefore many standardized principles and guidelines for clinical study design, conduct, data processing and analysis apply to diagnostic radiopharmaceuticals.
- Therapeutic radiopharmaceuticals are used to treat or manage a disease or condition. The drug development cascade and clinical platforms and expectations for other therapeutic drug products (i.e., pharmaceuticals or biologics) typically apply to therapeutic radiopharmaceuticals.

All information in the Clinical subsections apply to both diagnostic and therapeutic radiopharmaceuticals unless otherwise indicated.

Most radiopharmaceuticals are initially designed for the adult patient population. When a radiopharmaceutical is developed for pediatric use, appropriate age groups and patient populations should be considered with respect to radiation absorbed dose and other development components.

The clinical data package should consist of, and distinguish between, pivotal, non-pivotal, and other supportive trials. In these trials, the study design, results, and conclusions should follow GCP standards.

4.3.1. Pharmacodynamics and pharmacology

4.3.1.1. Primary pharmacodynamics

With respect to primary pharmacodynamics, the sponsor should provide:

- data from Phase I first in-human exposure studies that gather pharmacokinetic and initial safety assessments of the estimated mass dose and biodistribution of the product.

Pharmacodynamic aspects should be incorporated in Phase I studies when the product is intended to target specific receptors, metabolic processes, or other high affinity tissues or organs.

For diagnostics: Healthy volunteers may be studied in Phase I studies, unless toxicity or the radiation dose precludes such exposures.

For therapeutics: Patients with the disease or condition to be treated are studied in all phases of clinical trials because toxicity or radiation dose preclude such exposures to healthy subjects.

4.3.1.2. Secondary pharmacodynamics

With respect to secondary pharmacodynamics, the sponsor should provide evidence that pharmacokinetics, pharmacodynamics, and dose exposure-response relationships:

- support dose selection, including of the ligand where appropriate;

and

- substantiate any claims for a distinct lack of pharmacological effect
    - for diagnostics: in mass or activity for those doses;

    or
    - for therapeutics: of the ligand or lack of an adverse profile.

4.3.1.3. Pharmacology

With respect to pharmacology, the sponsor should provide:

- Phase II studies that verify the dosage regimen characterization, which are the clinically relevant and useful mass dose and radiation activity dose range claimed to be clinically useful and studied in later trials.

Note:

- Phase II studies should contribute to the pharmacokinetics and pharmacodynamics characterization, and allow opportunity to refine timing, techniques, and processes
    - for diagnostics: imaging;

    or
    - for therapeutics: fractionated therapy as relevant.
- Preliminary evidence should be collected about the safety and efficacy in patients.
- For diagnostics:
    - it is relevant to include subjects with and without known disease in order to help establish diagnostic performance;

    and
    - technical imaging quality should be studied.

4.3.2. Pharmacokinetics

4.3.2.1. Analytical methods and validation

With respect to analytical methods and validation, the sponsor should provide:

- information on the bioanalytical methods and validations used to assess concentrations of ligands or other components etc., in biological matrices;

and

- information on the methods used to assess radiation quantifications.

4.3.2.2. Absorption, distribution, metabolism, excretion

With respect to absorption, distribution, metabolism, and excretion of the drug product, the sponsor should provide:

- sufficient data from human biodistribution studies;

and

- sufficient data from internal dosimetry modelling;

to allow an estimation of radiation absorbed dose to the whole body and critical organs when the drug is administered.

With respect to biodistribution characterization, the sponsor should provide the assumptions and methodology used, including all sources of data, with detailed descriptions of models used in dosimetry calculations supporting dosing levels.

The sponsor should explain all considerations made for anticipated changes in dosimetry resulting from the presence of disease (e.g., renal dysfunction leading to a decreased renal excretion or hepatic dysfunction leading to a change in hepatobiliary clearance or other compensatory changes in paths of elimination).

- Note: specific patient populations may need to be studied to allow a claim for use in a specific patient population with an altered condition (e.g., use in renal failure).

The sponsor should provide a summary in table format of all relevant physical and biological parameters used in calculating each organ dose for all target organs and critical organs (organs at risk). Examples of parameters are:

- the fractional uptake of administered radioactivity into each organ;
- the biological half-life in each organ;

and

- the contribution to absorbed dose from the principal radionuclide and all relevant radiochemical and radionuclidic impurities as presented by the sponsor's data and computations. Data should typically reflect that of an average adult human after the administration of the recommended radioactive dose (activity) of the radiopharmaceutical.

The sponsor should list operational definitions and verify corresponding units of expression when citing terminology, value declarations, or units of expression e.g., equivalent dose versus effective dose data presentations.

4.3.3. Radiation dosimetry

This introduction provides sponsors with key general information that underlies the radiation dosimetry specific submission data requested in the subsections below.

Biodistribution and dosimetry estimates in humans are expected for the authorization of radiopharmaceuticals by Health Canada. However, under certain circumstances when the dosimetry assessment may not be feasible (e.g., radiopharmaceuticals for

radiolabelling not intended to be directly administered to patients such as In-111 chloride), these situations can be assessed on a case-by-case basis.

The radiation absorbed dose estimates characterized from human data are then used to substantiate and verify the safety and efficacy profile which characterizes the conditions of use of the product.

In certain circumstances when sufficient original data is not available, the above requirements may instead be addressed by other means e.g., third-party data.

These situations would be assessed on a case-by-case basis.

With respect to providing radiation dosimetry estimates in humans, the sponsor should use the MIRD schema to estimate the absorbed dose (i.e., the concentration of energy deposited in the tissue or organ) in each organ or tissue. The sponsor:

- may refer to the most recent ICRP guidance on MIRD schema for dosimetry calculation;
- should use the most recent updated data on tissue and radiation weighting factors and nuclear decay data as per ICRP;
- should consider using reference phantoms for dosimetry calculation as recommended by ICRP;

and

- should consider using models and software that incorporate the most recent changes from ICRP e.g., the latest version of OLINDA/EXM.

The sponsor should also provide data for the maximum and minimum recommended dose/activity, including instances when dosing is individualized on a per metres squared or per kg basis.

4.3.3.1. Biodistribution, corroborating data, assumptions, and models

With respect to biodistribution and corroborating data for radiation absorbed dose estimates, the sponsor should provide:

- all sources of data from animal biodistribution studies used to calculate radiation absorbed dose estimates;
- a description of models used in radiation absorbed dose estimates calculations;

and

- an analysis of all assumptions used in any dose calculation.

With respect to radiation absorbed dose estimates in animal models, the sponsor should provide:

- a summary of dose estimates;
- a presentation of corroborating data (parameters, assumptions, models, etc.) used to calculate the dose estimates;

- dose estimates calculated from biodistribution data;

and

- estimates of the equivalent dose or the effective dose or both, per unit administered activity (mSv/MBq and mrem/mCi) for each phantom.

With respect to the characterization of radiation dosimetry, the sponsor should provide:

- a summary of dose estimates;

and

- a presentation of corroborating data (parameters, assumptions, models, etc.) used to calculate the final dose estimates.

Presentation of the raw data used to derive the parameters should be available upon request.

4.3.3.2. Summary of radiation dose estimates

With respect to radiation absorbed dose estimates, the sponsor should provide:

- dose estimates based on human data used in the calculations, whereas supportive animal data would be included in the non-clinical section;
- estimates of the equivalent dose (i.e., how much biological change is expected from the absorbed dose). Note that the radiation weighting factor equals 1 for gamma and beta emitters;
- data estimates when phantoms are used;

and

- the effective dose (i.e., to assess the potential for long-term effects that might occur in the future) per unit administered activity (mSv/MBq and mrem/mCi).

Note that the effective dose is a calculated value that takes into account the absorbed dose to all organs of the body, the relative harm level of the radiation, and the sensitivities of each organ to radiation. It may be used to assess comparative radiation exposure.

The sponsor should provide overall radiation dose estimates that include:

- the radionuclide used in the formulation of the drug (i.e., the principal radionuclide);

and

- any radiochemical or radionucludic impurities that may contribute substantially to the total effective dose.

These inclusions can help characterize the absorbed dose that may be impacted by such impurities, and is a means to help account for contributions to the total radiation burden e.g., effective dose.

In the case of hybrid imaging with PET/CT or SPECT/CT, the sponsor should provide estimates for:

- the radiation exposure from the CT component of the imaging procedure;

and

- the total effective dose provided for the imaging procedure.

Generally, the sponsor should provide data to demonstrate that the clinical effective dose is the smallest radiation absorbed dose to allow, in the case of a diagnostic radiopharmaceutical, the greatest diagnostic performance or in the case of a therapeutic radiopharmaceutical, the desired therapeutic effect (i.e., the ALARA, "as low as reasonably achievable" principle).

4.3.3.3. Presentation of data

With respect to the presentation of data, the sponsor should present absorbed doses:

- in the ICRP format;

and

- in tabular summaries, where relevant, of the cumulative organ-absorbed radiation dose estimates from the radiopharmaceutical, and radionuclidic and radiochemical impurities that might be present in the final dosage form, expressed in mGy/MBq and mrad/mCi per unit activity injected.

The sponsor should also present the data using:

- the equivalent dose;

and

- effective dose per unit administered activity (mSv/MBq and mrem/mCi).

The following is a sample table for the presentation of final dose estimate data, where the sponsor should specify:

- the model and method used for calculation;
- human data used in the calculations, whereas supportive animal data would be included in the non-clinical section;
- supporting discussion or data or both, in terms of the potential for influence of pathophysiological changes induced by disease processes e.g., organs that are critical in metabolism or excretion of the radiopharmaceutical;
- when relevant, any additional information pertinent to the final dose estimates presented in the table, e.g., whether thyroid block was or was not used;
- for radiopharmaceuticals intended for pediatric uses, radiation dose estimates should be presented for the standard anthropomorphic

phantoms as per the ICRP i.e., 15-year old, 10-year old, 5-year old, 1-year old, newborn;

and

- if the tabulated data is cited from the ICRP, this should be stated and referenced.

Organ	Absorbed dose per unit administered activity (mGy/MBq)	Absorbed dose per unit administered activity (rad/mCi)
-	-	-
-	-	-
Effective Dose (mSv/MBq)(rem/mCi)	-	-

4.3.4. Safety and efficacy studies

With respect to safety and efficacy studies, the sponsor should provide the same general submission data for radiopharmaceutical drugs as for non-radiopharmaceutical drugs, because the usual drug development cascade applies to all clinical trial phases for radiopharmaceutical drugs.

The sponsor should provide certain radiopharmaceutical-specific submission data for Phase I and II studies as set out below, where differences for diagnostic and therapeutic radiopharmaceuticals are indicated.

Phase I studies are, generally, the first in-human exposure of the drug, that assesses pharmacokinetics and initial safety taking into account mass dose and biodistribution; and that assesses pharmacodynamics where the drug is intended to target specific receptors or metabolic processes. A difference between diagnostic and therapeutic radiopharmaceuticals is that

- for diagnostic radiopharmaceuticals: healthy volunteers would participate in Phase I CTAs, unless toxicity or radiation dose preclude exposure to healthy volunteers;

whereas

- for therapeutic radiopharmaceuticals: patients are studied in all CTA phases because toxicity and radiation dose preclude healthy volunteers from being exposed.

Phase II studies determine, generally, the dosage regimen characterization of the drug, to refine or verify the clinically relevant and useful mass dose and radiation activity dose range to be studied in later Phase III studies.

Phase II studies support pharmacokinetics and pharmacodynamics characterization, and allow the refining of timing, techniques, and processes

- for diagnostic radiopharmaceuticals: for imaging;

or

- for therapeutic radiopharmaceuticals: for fractionated therapy.

Phase II studies also show preliminary evidence of safety and efficacy in humans

- for diagnostic radiopharmaceuticals: to establish and assess diagnostic parameter performance, the sponsor should provide:
  - data from subjects with and without known disease;

  and
  - data that shows technical imaging quality.

Phase III studies are, generally, larger scale trials that establish efficacy and more thoroughly characterize the safety profile of the drug in a well-defined target population under intended conditions and indications of actual clinical use. The design of Phase III studies reflects data and information from Phase II studies. Phase III studies are generally based on data from the drug formulation intended for marketing, where bridging studies should be provided in absence of data from the drug formulation intended for marketing. Multiple efficacy studies or multi-centered studies are often performed to increase the generalizability of the accrued data and results to the intended actual use and product performance profile.

4.3.4.1. Pivotal trials

With respect to pivotal trials, the sponsor should provide the following submission data. Note that diagnostic and therapeutic radiopharmaceuticals do not present many differences with respect to submission data, except those indicated in the Guidance document. Therapeutic radiopharmaceuticals generally follow what is recommended for therapeutic drugs.

With respect to indications and intended clinical use, the sponsor should provide evidence to show that the design and conduct of clinical trials substantiate the claims.

With respect to effectiveness, the sponsor should provide evidence to show that the efficacy of the drug is well established, and that the clinical benefit of the drug is demonstrated

- for diagnostic radiopharmaceuticals: to establish clinical value of the drug, the sponsor should provide data to demonstrate that the drug provides accurate and reliable information about the clinical disease or condition.

Therapeutic radiopharmaceuticals should be evaluated the same as other therapeutic drugs.

With respect to the design, conduct, and analysis of trials, the sponsor should state in the protocol the trial objectives, trial populations to be studied, and the

trial endpoints (primary and secondary), which are all supported by an adequate statistical analysis plan. Please see Section 4.3.5 - Biostatistics. Specific factors to be considered include, but are not limited to

- for diagnostic radiopharmaceuticals:
    - diagnostic performance – diagnostic performance characterizes the sensitivity and specificity of the test under conditions studied or conditions of clinical use by comparing against a standard of truth. This is intended to support how the diagnostic radiopharmaceutical reflects the reality or truth as associated with a measurement or method that is regarded as the standard of truth or gold standard. When a standard of truth cannot be used or is unavailable, the sponsor should consult Health Canada in advance of the submission to address concerns regarding evidence of efficacy and clinical benefit.
    - technical performance – to establish and characterize the technical performance, the sponsor should provide data on concordance between multiple readers, and reproducibility of results. When applicable, the sponsor should provide comparison data with other diagnostic modalities;

    and
    - clinical benefit – the sponsor should provide information on how the use of the diagnostic radiopharmaceutical impacts patient management decisions;
- for therapeutic radiopharmaceuticals:
    - non-inferiority or superiority trial designs;
    - how the drug fits into existing and established therapeutic cascades, which may involve concomitant use with other non-radiotherapeutic drugs;
    - long-term safety effects when the drug is used for anticipated life-sustaining interventions, but not in the case where the drug is intended exclusively for symptom management, like pain palliation, in end-stage terminal illness;

    and
    - impact of the radiotherapeutic drug on subsequent patient management alternatives i.e., impact on options for subsequent lines of therapy, on possible repeat courses of therapy on advanced disease, on posssible relapse, etc.

4.3.4.2. Non-pivotal trials

For non-pivotal trials, the sponsor should provide, when available, data to support safety characterization or other product development initiatives and goals.

Non-pivotal trials typically help establish safety or dosing or both, in patients with the disease to be diagnosed or treated, and the data from the trials is only supportive of safety and efficacy claims.

4.3.4.3. Other clinical studies

With respect to clinical trials other than pivotal or non-pivotal, the sponsor should provide data that supports product development, such as:

- data from special populations e.g., elderly, pediatrics, or hepatic or renal insufficiency patients;
- data from trials for which the indication will not be pursued, but which can contribute safety data;

or

- data from a bridging study when formulation changes have been made during clinical trials.

4.3.4.4. Other information

In addition to the submission data requested above, the sponsor may provide other published information to support their safety and efficacy studies e.g.,

- data from published literature that is reviewed and assessed using a systematic or meta-analysis approach;
- data from original articles published in peer-reviewed journals and sourced from multiple labs, research centres, or academic centres i.e., published data that is valid and supported by the scientific community. The data should be supportive of submissions, and should represent a raw material of interest (i.e., associated with the drug substance or ligand), since such data is not usually generated for the specific formulation under development (i.e., the drug product). Because differences in manufacturing between the specific formulation and published data may impact quality (e.g., the impurity profile of the ligand, and radionuclidic and radiochemical purity of the radiopharmaceutical) or final specifications of the drug product, published data is typically supportive and complements submission data;
- data with the specific drug development process taken into account, as differences in manufacturing and production may have an impact on quality (e.g., the impurity profiles of the ligand and radionuclide) or final specifications;

or

- in certain instances, third-party data may be the primary support in the submission for safety and efficacy (see Section 6.1.1 for third party data).

4.3.5. Biostatistics

The relevant principles outlined in ICH E9 and ICH E10 should be considered as needed in this section.

With respect to biostatistics for diagnostic radiopharmaceuticals, the sponsor should:

- provide a study protocol,
    - which gives details on the study objectives, study design, definition and establishment of the gold standard, diagnostic parameters to be assessed, and statistical methods;
    - which discusses measures to avoid or minimize bias;

    and
    - which is finalized before the start of the study, and where any changes to the protocol are introduced in a formal amendment to the protocol;
- specify in the protocol, with regard to diagnostic parameters, those that are critical to be evaluated e.g., sensitivity, specificity, and accuracy of the diagnostic radiopharmaceutical relative to the gold standard;
- ensure that blinded readers are used to interpret images, and provide information to support this in the protocol. If multiple readers are used, the protocol should state whether the assessment of diagnostic parameters is based on each individual reader or on a majority read. If the latter, then the level of agreement amongst the different readers should be assessed, and the method for assessing the level of agreement should be described in the protocol. The handling of equivocal readings should be specifically addressed in the protocol, as should be the handling of missing or spurious data;
- provide a justification for the selected number of patients, ensuring that a sufficient number of both diseased and non-diseased patients are included in the study to allow sensitivity and specificity to be estimated with a high degree of precision;
- provide reference values in the protocol for comparing the diagnostic parameter estimates from the current study, which should be based on a well-planned and executed systematic review and meta-analysis of the relevant literature;

and

- provide details on the statistical approach that will be used to compare the diagnostic parameter estimates from the current study to the reference values derived from the literature specified in the protocol, including the success criteria for the study.

With respect to biostatistics for therapeutic radiopharmaceuticals, the sponsor should:

- provide the trial protocol,
    - which gives details on the trial's design, conduct, and statistical analysis;

- which discusses measures to avoid or minimize bias, especially in open label trials with subjective endpoints;
- which provides some assurance that the protocol, as proposed, results in sufficient data of high quality to allow a meaningful assessment of the efficacy and safety of the therapeutic radiopharmaceutical;
- which is finalized before the start of the trial, and where there are justifications and documentation for any subsequent amendments to the protocol;
- where the critical study design aspects are captured in the trial protocol e.g., the specific design for a given trial, the selected primary endpoint or endpoints if multiple primary endpoints are proposed, and the secondary endpoints;
- which documents the role of the secondary endpoints in the overall interpretation of the trial results;

and

- which states whether the trial is designed to show superiority to the selected comparator, or is designed to show non-inferiority or equivalence, as per ICH guiding principles (see Section 6.4.2.1 – Reference 1);

- provide a Statistical Analysis Plan (SAP),
  - which documents the technical details regarding the statistical methodology to be applied in the trial and should be finalized prior to the un-blinding of the trial data. Any amendments to the SAP should also be finalized prior to the un-blinding of the trial data;
  - which is consistent with ICH statistical principles (see Section 6.4.2.1 – Reference 2);

  and

  - where the handling of missing data and early withdrawals from the trial, and the control of the Type 1 error rate due to multiple testing, are well described;

and

- address additional considerations depending on the type of endpoints evaluated.
  - For instance, the use of tumour-based endpoints that are “time-to-event” in nature, such as progression-free survival, creates unique challenges; therefore, special attention should be paid to the collection, reporting, and analysis of such endpoints. Refer to FDA information on tumour-based endpoints (see Section 6.4.2.2 – United States Food and Drug Administration (FDA)).
  - In the case of therapeutic radiopharmaceuticals intended for pain palliation using subjective self-reported pain outcomes, the sponsor should provide evidence that the specific tool selected for assessing pain has been validated in a similar population to the population being evaluated in the current trial. The sponsor should also provide evidence that measures to minimize bias in the reporting of subjective

pain outcomes have been put in place at the start of the trial. The sponsor should additionally:

- provide a discussion of the clinical utility of the specific endpoint selected to demonstrate the effect of the therapeutic radiopharmaceutical on pain;
- provide instructions on the use of concomitant analgesics permitted in the protocol;

and

- ensure that detailed information on the use of any additional pain medications is collected, recorded, and appropriately analyzed. The sponsor should then provide results from an assessment of the impact of additional pain medication on the primary and secondary outcome measures.

5. SECTION ANDS - SUBMISSION DATA SPECIFIC TO SCHEDULE C DRUGS FOR ABBREVIATED NEW DRUG SUBMISSIONS

See Section 2 - How to use this document for a description of how to jump forwards and backwards from the sub-Table of Contents for the ANDS section.

The overview of SECTION ANDS is:

The Abbreviated New Drug Submission (ANDS) is for the sponsor who seeks market authorization based on pharmaceutical equivalence to a previously approved Schedule C drug, and relies in part on prior information regarding that Schedule C drug in order to present a reduced clinical and non-clinical package as part of the submission. For the eligibility criteria of an ANDS, please see Section C.08.002.1(1), in Division 8 (New Drugs), in Part C (Drugs), in the *Food and Drug Regulations*, in Canada's *Food and Drugs Act*, on the Government of Canada's Justice website.

The ANDS submission must demonstrate that the drug product is the generic version of a Canadian Reference Product (CRP), in terms of production, formulation, specifications/strength, dosage form, and quality control including shelf-life of the final product. For the eligibility criteria of a CRP, please see Section C.08.001.1, in Division 8 (New Drugs), in Part C (Drugs), in the *Food and Drug Regulations*, in Canada's *Food and Drugs Act*, on the Government of Canada's Justice website.

5.1. QUALITY SUBMISSION DATA

Quality submission data is outlined in this Guidance document based on the Schedule C drug's emission characteristics (GERs, PERs, NGNPs) or how the Schedule C drug is manufactured (generators, kits).

5.1.1. Gamma-emitting radiopharmaceuticals (GERs)

A gamma-emitting radiopharmaceutical (GER) is a Schedule C drug that contains a gamma emitter, is pre-radiolabelled as a final drug product and is supplied in a ready-to-use dosage form. The GER is not further manipulated prior to administration of the product in patients, other than to measure the radioactive dose, pH, and perform radiochemical purity analysis, according to the PM.

The name of the CRP to which the product is compared must be identified.

Note on how to navigate 2 of the subsections that follow:

- If the GER contains a drug substance of chemical origin that is radiolabelled with a radionuclide, then both Section 5.1.1.2 - Drug substance synthesis and purification, and Section 5.1.1.3 - Radionuclide source and production apply;

and

- If the GER contains only the radionuclide or radiochemical, then only Section 5.1.1.3 - Radionuclide source and production applies e.g., when the GER is used in radiolabelling of a kit.

5.1.1.1. Source

With respect to source, the sponsor should:

- list the names and addresses of all facilities involved in the manufacture, packaging, labelling, and testing of the radionuclide, precursor or ligand, API or drug substance or both, and drug product.

5.1.1.2. Drug substance synthesis and purification

With respect to drug substance synthesis and purification, the sponsor should provide:

- a list of all raw materials, and a list of all starting materials, each of the materials with their C of A either from the vendor or generated in-house;
- details on synthesis, purification, and the structure elucidation process, including quality controls, specifications, and a flow chart identifying reaction yield;
- a side-by-side comparison of the drug substance's specifications to that of the CRP;
- stability data under accelerated and real-time storage conditions in support of the claimed shelf-life;
- stability data for at least 3 consecutive commercial-scale batches;
- stability data generated at both upright and inverted orientations; or a rationale if data for only 1 orientation has been generated e.g, lyophilized pellet;

and

- the recommended shelf-life and its supporting study conditions and study duration.

Packaging should follow all applicable standards for the product type.

Labelling must follow the regulatory requirements referenced in Section 6.3 - Key legal references.

5.1.1.3. Radionuclide source and production

With respect to radionuclide source and production, the sponsor should provide:

- information on the radionuclide synthesis process, including details about the cyclotron, accelerator, reactor, or generator used; when applicable, a DMF should be submitted or cross-referenced or both;
- detailed information on the target, including target body; information on other raw materials should be submitted if not included in the DMF;
- C of A for the target material either from the vendor or generated in-house;
- comparative specifications of the radionuclide with that of the radionuclide used in the CRP;
- analysis of radionuclidic, radiochemical, and chemical purity and impurity;

- analysis of target breakthrough in the final radionuclide (i.e., desired product) such as Mo-100 in Tc-99m made directly via cyclotron or accelerator;

and

- if the radionuclide is used in manufacturing to radiolabel ligands, then data should be generated for kits containing anionic, cationic, and neutral ligands if the radionuclide is intended to radiolabel kits or other ligands.

5.1.1.4. Development pharmaceutics

This section exists for CTA and NDS only, and is not applicable to ANDS.

5.1.1.5. Formulation and drug product manufacturing

With respect to formulation and drug product manufacturing, the sponsor should provide:

- a table identifying all ingredients and their role(s) in the formulation; when possible, include a table comparing the formulation of the drug product to that of the CRP;
- detailed information on the manufacturing process, including radiolabelling, purification, vial filling, vial stoppering, and packaging;
- quality control and batch analyses data, batch production records, and comparative release specifications of the final product and the CRP;
- SOPs for all analytical procedures with their validation study data;

and

- shipping validation data covering the furthest distance simulating the real-life commercial supply; or if not possible, a statement that the end user is responsible for performing stability indicating tests i.e., the percentage of radiochemical purity, the pH, and the appearance of the final drug product as set out in the PM.

5.1.1.6. Stability and packaging

With respect to product stability and compatibility with packaging materials which are in direct contact with the drug product (e.g., vials, stoppers), the sponsor should provide stability data:

- for 3 consecutive commercial-scale batches using accelerated and real-time storage conditions;
- generated at both upright and inverted orientations;

and

- to support a comparable recommended shelf-life for the drug product to that of the CRP.

Packaging should follow all applicable standards for the product type.

Labelling must follow the regulatory requirements referenced in Section 6.3 - Key legal references.

5.1.1.7. Pharmaceutical comparability and equivalency

With respect to the demonstration of radiopharmaceutical comparability or equivalency of the drug product and the CRP, the sponsor should provide:

- formulation comparability data;
- specifications comparability data for the drug product;
- manufacturing comparability data for the drug product;
- stability and storage conditions data for the drug substance and drug product;

and

- packaging materials data for the drug product, including vial and stoppers.

5.1.2. Positron-emitting radiopharmaceuticals (PERs)

A positron-emitting radiopharmaceutical (PER) is a Schedule C drug that contains a cyclotron-produced positron emitter. One of the most common PERs is Fluorine-18 (F-18) labelled Fluorodeoxyglucose (FDG).

The name of the CRP to which the product is compared must be identified.

Note:

- PERs that are manufactured using radionuclide generators are not addressed in Section 5.1.2 - Positron-emitting radiopharmaceuticals (PERs), but are addressed in Section 5.1.4 - Generators.

5.1.2.1. Source

With respect to source, the sponsor should:

- list the names and addresses of all facilities involved in the manufacture, packaging, labelling, and testing of the radionuclide, precursor or ligand, API or drug substance or both, and drug product.

5.1.2.2. Precursor, ligand, or drug substance source and synthesis

With respect to the source and synthesis of the precursor or ligand, the sponsor should indicate if the precursor or ligand is available commercially, synthesized in-house, or synthesized by a contract manufacturer.

If the precursor or ligand is a commercial product (e.g., mannose triflate), the sponsor should provide the name and C of A from the vendor, including storage conditions and expiry date.

Whether the precursor or ligand is synthesized by the sponsor or a contract manufacturer, the sponsor should provide:

- a list of all raw materials, and a list of all starting materials each with their C of A either from the vendor or generated in-house;
- details on synthesis, purification, and structure elucidation process of the precursor or ligand, including a flow chart with reaction yield, quality control, and specifications;
- a stability data comparison between the precursor or ligand and the CRP;
- stability data for at least 3 consecutive commercial-scale batches;
- stability data generated at both upright and inverted orientations; or a rationale if data for only 1 orientation has been generated;

and

- the recommended shelf-life and its supporting study conditions and study duration.

Packaging should follow all applicable standards for the product type.

Labelling must follow the regulatory requirements referenced in Section 6.3 - Key legal references.

5.1.2.3. Radionuclide source and production

With respect to radionuclide source and production, the sponsor should provide:

- information about the cyclotron used e.g., type, size or capacity, target size, target body type, beam current and irradiation time;
- detailed information on the target e.g., enrichment level, vendor name with the C of A;
- information on enrichment level and procedure with respect to whether the target is reused or recycled;
- information about the radionuclide production or synthesis process; when applicable, a DMF should be submitted or cross-referenced or both;
- information about other raw materials used for processing or purification beyond the scope of the DMF;
- a side-by-side comparison of the radionuclide's specifications to that of the radionuclide used in the CRP;

and

- in the case where the radionuclide is imported, information about the shipping process and further manufacturing, including details of the processing on receipt at the site prior to use in radiosynthesis.

5.1.2.4. Development pharmaceutics

This section exists for CTA and NDS, and is not applicable to ANDS.

5.1.2.5. Formulation and drug product manufacturing

With respect to formulation and drug product manufacturing the sponsor should provide:

- a quantitative formulation table for a batch and unit vial, including the radioactivity range (in MBq or mCi), identifying all ingredients and their roles in the formulation; additionally when possible, the sponsor should provide a comparative table of the formulation of the final product and the CRP;
- details of the manufacturing process with respect to the Automated Synthesis Unit or Semi-Automated Synthesis Unit or manual radiolabelling; the deprotection and purification processes including radiochemical yield at the end of synthesis;
- details of the vial filling, stoppering, labelling, and packaging;
- for ASU or S/ASU, the type of cartridge or manifold used, and its vendor information;
- quality control and batch analyses data, batch production data, and comparative release specifications of the final product with that of the CRP; additionally, the sponsor should indicate which tests are done prospectively, and which tests are done retrospectively;
- SOPs for all analytical procedures with their validation study data;

and

- shipping validation data covering the furthest distance simulating the real-life commercial supply; or if not possible, a statement that the end user is responsible for performing stability indicating tests i.e., the percentage of radiochemical purity, the pH, and the appearance of the final drug product as set out in the PM.

5.1.2.6. Stability and packaging

With respect to product stability and compatibility with packaging materials which are in direct contact with the drug product (e.g., vials, stoppers), the sponsor should provide stability data:

- for 3 consecutive commercial-scale batches using accelerated and real-time storage conditions;
- generated at both upright and inverted orientations; or a rationale if data for only 1 orientation has been generated;

and

- that compares the recommended shelf-life of the drug product and that of the CRP.

Packaging should follow all applicable standards for the product type.

Labelling must follow the regulatory requirements referenced in Section 6.3 - Key legal references.

5.1.2.7. Pharmaceutical comparability and equivalency

With respect to the demonstration of radiopharmaceutical comparability or equivalency of the drug product and the CRP, the sponsor should provide:

- formulation comparability data;
- specifications comparability data for the drug product;
- manufacturing comparability data for the drug product, including the production of the radionuclide, the radiosynthesis procedures (e.g., the type of Automated Synthesis Unit (ASU) cartridge or manifold used), and the purification process;
- stability and storage conditions data for the drug substance, precursor, ligand, and drug product;

and

- packaging materials data for the drug product, including vial and stoppers.

5.1.3. Non-GERs non-PERs radiopharmaceuticals (NGNP)

A non-GERs non-PERs radiopharmaceutical (NGNP) is a Schedule C drug produced by a linear accelerator or nuclear reactor. NGNPs include alpha emitters and negatron emitters (beta minus). NGNPs include, but are not limited to, radionuclides such as Astatine-211 (As-211), Iodine-131 (I-131), Lutetium-177 (Lu-177), Radium-223 (Ra-223), Rhenium-188 (Re-188), Samarium-153 (Sm-153), Thorium-227 (Th-227), and Yttrium-90 (Y-90).

The name of the CRP to which the product is compared must be identified.

Note on how to navigate 2 of the subsections that follow:

- If the NGNP contains a drug substance of chemical origin that is radiolabelled with a radionuclide, then both Section 5.1.3.2 - Drug substance synthesis and purification, and Section 5.1.3.3 - Radionuclide source and production apply;

and

- If the NGNP contains only the radionuclide or radiochemical, then only Section 5.1.3.3 - Radionuclide source and production applies.

5.1.3.1. Source

With respect to source, the sponsor should:

- list the names and addresses of all facilities involved in the manufacture, packaging, labelling, and testing of the radionuclide, precursor or ligand, API or drug substance or both, and drug product.

5.1.3.2. Drug substance synthesis and purification

With respect to drug substance synthesis and purification, the sponsor should provide:

- a list of all raw materials, and a list of all starting materials each with their C of A either from the vendor or generated in-house;
- details on synthesis, purification, and the structure elucidation process, including quality controls, specifications, and a flow chart identifying reaction yield;
- stability data under accelerated and real-time storage conditions in support of the claimed shelf-life;
- stability data for at least 3 consecutive commercial-scale batches;
- stability data generated at both upright and inverted orientations; or a rationale if data for only 1 orientation has been generated;

and

- the recommended shelf-life and its supporting study conditions and study duration.

Packaging should follow all applicable standards for the product type.

Labelling must follow the regulatory requirements referenced in Section 6.3 - Key legal references.

5.1.3.3. Radionuclide source and production

With respect to radionuclide source and production, the sponsor should provide:

- information on the radionuclide synthesis process, including details about the cyclotron, accelerator, reactor, or generator used; when applicable, a DMF should be submitted or cross-referenced or both;
- detailed information on the target, including target body; information on other raw materials should be submitted if not included in the DMF;
- C of A for the target material from either the vendor or generated in-house;
- specifications of the radionuclide;
- analysis of radionuclidic, radiochemical, and chemical purity and impurity;
- analysis of target breakthrough in the final radionuclide (i.e., desired product) such as Te-131 in I-131, or W-188 in Re-188, or Re-185 in Re-186, produced by a linear accelerator;

and

- radiolabelling data if the radionuclide is intended to radiolabel kits or other ligands.

5.1.3.4. Development pharmaceutics

This section exists for CTA and NDS only, and is not applicable to ANDS.

5.1.3.5. Formulation and drug product manufacturing

With respect to formulation and drug product manufacturing, the sponsor should provide:

- a quantitative formulation table for a batch and unit vial, including the radioactivity range (in MBq or mCi), identifying all ingredients and their roles in the formulation;
- detailed information on the manufacturing process, including radiolabelling, purification, vial filling, vial stoppering, and packaging;
- batch analyses data and batch production records with release specifications for at least 3 commercial-scale batches of the final product; additionally, the sponsor should indicate which tests are done prospectively, and which tests are done retrospectively; finally, the sponsor should provide quality control and batch analyses data, batch production records, and comparative release specifications of the final product and the CRP;
- SOPs for all analytical procedures with their validation study data;

and

- shipping validation data covering the furthest distance simulating the real-life commercial supply; or if not possible, a statement that the end user is responsible for performing stability indicating tests i.e., the percentage of radiochemical purity, the pH, and the appearance of the final drug product as set out in the PM.

5.1.3.6. Stability and packaging

With respect to product stability and compatibility with packaging materials which are in direct contact with the drug product (e.g., vials, stoppers), the sponsor should provide stability data:

- for 3 consecutive commercial-scale batches using accelerated and real-time storage conditions;
- generated at both upright and inverted orientations;

and

- to support a comparable recommended shelf-life for the drug product to that of the CRP.

Packaging should follow all applicable standards for the product type.

Labelling must follow the regulatory requirements referenced in Section 6.3 - Key legal references.

5.1.3.7. Pharmaceutical comparability and equivalency

With respect to the demonstration of radiopharmaceutical comparability or equivalency of the drug product and the CRP, the sponsor should provide:

- formulation comparability data;
- specifications comparability data for the drug product;
- manufacturing comparability data for the drug product;
- stability and storage conditions data for the drug substance and drug product;

and

- packaging materials data for the drug product, including vial and stoppers.

5.1.4. Generators

A generator is defined in Part C, Division 3 of the *Food and Drug Regulations* (C.03.001).

A generator typically contains a column with a large amount of a radionuclide (i.e., parent radionuclide) that decays down to a second radionuclide of shorter half-life (i.e., daughter radionuclide). The daughter radionuclide is separated from the parent by the process of elution, which gives a continuing supply of relatively short-lived radionuclides.

5.1.4.1. Source

With respect to source, the sponsor should:

- list the names and addresses of all facilities involved in the manufacture, packaging, labelling, and testing of the radionuclide, precursor or ligand, API or drug substance or both, and drug product.

5.1.4.2. Parent radionuclide and processing

With respect to the parent radionuclide and its processing, the sponsor should provide:

- general information about the production, properties, and quality control of the parent radionuclide e.g., C of A for radionuclidic, radiochemical, and chemical purity and impurities, specific activity, activity concentration, pH, appearance, etc.;
- detailed information about the accelerator or reactor used. Alternatively, the sponsor should cross-reference a DMF;

- detailed information about the target or target body. Additionally, the sponsor should provide detailed information about other raw materials when not included in the DMF;

and

- specifications of the radionuclide compared to those of the radionuclide used in the CRP.

5.1.4.3. Development pharmaceutics

This section exists for CTA and NDS, and is not applicable to ANDS.

5.1.4.4. Formulation and generator manufacturing process

With respect to formulation and generator manufacturing process, the sponsor should provide:

- the names and addresses of all facilities involved in the production and processing of the parent radionuclide and the generator;
- the formulation and production methodology of the generator, including total radioactivity of the generator, type and source of adsorbent, tubing, sterile filter, collection vial etc.;
- in the case where the eluate is for direct administration, details about dose preparation i.e., volume, specific activity, total radioactivity, radioactive concentration, and other appropriate data;
- specifications for the final product (i.e., the eluate) which should at least include appearance, radionuclidic purity, radiochemical purity, percentage of parent radionuclide breakthrough or radioactive amount present (in MBq or mCi) and the amount of adsorbent material present, pH, and osmolality;
- confirmation of which quality control test parameters are done at release, and which are done retrospectively;
- batch analysis data, including data for tests done retrospectively, for at least 3 consecutive batches;

and

- in the case where the daughter radionuclide radiolabels kits or other ligands, radiolabelling data for kits containing anionic, cationic, and neutral ligands. If the radionuclide is only to be used to radiolabel a specific kit or ligand, then the sponsor should provide radiolabelling data for that particular kit or ligand.

5.1.4.5. Stability and packaging

With respect to stability and packaging, the sponsor should provide, for 3 consecutive commercial-scale batches:

- data to support generator stability for the column, including for parent radionuclide and column adsorbent breakthrough throughout the

shelf-life of the generator, and its eluate specifications for percentage of radiochemical purity, percentage of radionuclidic purity, pH, and appearance;
- data to support the expiry date of the eluate at post-elution, including storage conditions;
- data to support stability associated with compatibility of the vial content with the container closure i.e., a study performed by storing at the upright and inverted orientations for up to the proposed expiry period;
- when available, a side-by-side comparison of data with that of the CRP generator for all above listed studies;

and
- information that shows that packaging is according to generator type and size with required shielding as specified by the CNSC.

Packaging should follow all applicable standards for the product type.

Labelling must follow the regulatory requirements referenced in Section 6.3 - Key legal references.

5.1.4.6. Pharmaceutical comparability and equivalency

With respect to the demonstration of radiopharmaceutical comparability or equivalency of the drug product and the CRP, the sponsor should provide:
- formulation comparability data;
- production and specifications comparability data for the parent radionuclide;
- manufacturing and specifications comparability data for the generator and eluate e.g., column type, adsorbent used, parent radionuclide and adsorbent breakthrough, pH, appearance, radiochemical and radionuclidic purity, etc.;
- kit radiolabelling comparability data using anionic, cationic, and neutral ligands, including appearance, pH, radiochemical purity and impurity, and stability of the radiolabelled product;

and
- packaging materials data for the generator, including generator accessories.

5.1.5. Kits

A kit is defined in Part C, Division 3 of the *Food and Drug Regulations* (C.03.205).

A kit is a Schedule C drug that is used in the preparation of a radiopharmaceutical.

5.1.5.1. Source

With respect to source, the sponsor should:

- list the names and addresses of all facilities involved in the manufacture, packaging, labelling, and testing of the API or drug substance, and drug product.

5.1.5.2. Drug substance synthesis and purification

With respect to drug substance synthesis and purification, the sponsor should provide:

- a list of all raw materials, and a list of all starting materials each with their C of A either from the vendor or generated in-house;
- details on synthesis, purification, and the structure elucidation process, including quality controls, specifications, and a flow chart identifying reaction yield;
- a side-by-side comparison of the drug substance's specifications to that of the CRP;
- a stability data comparison between the drug substance and the CRP under accelerated and real-time storage conditions;
- the DMF obtained from the supplier, in the case where the drug substance is manufactured by a contract manufacturer;

and

- shipping validation data in the case where the product is shipped from off-site, including specific shipping information for thermolabile or photosensitive products.

5.1.5.3. Development pharmaceutics

This section exists for CTA and NDS only, and is not applicable to ANDS.

5.1.5.4. Formulation and drug product manufacturing

With respect to formulation and drug product manufacturing, the sponsor should provide:

- a table identifying all ingredients and their roles in formulation. When possible, the sponsor should provide a comparative table for the formulation of the CRP;
- detailed information on the manufacturing process, including purification, vial filling, vial stoppering, lyophilization, and packaging;
- quality control and batch analyses data, comparative release specifications with the CRP, and batch production records that include release specifications for the radiolabelling method and analysis of percentage of radiochemical purity and impurities for the following 3 situations:

- using a radionuclide from a source approved in Canada or an eluate from a generator approved in Canada;
- obtaining Tc-99m or other gamma-emitting radionuclides from a generator. In this situation, the sponsor should additionally provide data that demonstrates that conditions, such as when the eluate is more than 2 hours old and from a generator not eluted for more than 72 hours, do not affect the desired radiolabelling yield, nor the radiochemical purity and impurity profiles;

or

- obtaining radionuclides other than Tc-99m from a generator (e.g., Re-186). In this situation, the sponsor should additionally provide data that demonstrates that conditions do not affect the desired radiolabelling yield, nor the radiochemical purity and impurity profiles e.g., placing limits on the expiry of the eluate related to when the generator was last eluted, or when the generator is not eluted in the specified time;
    - If the second situation listed above is not met, the sponsor should state in the PM the generator-specific conditions with the eluate-specific conditions, such as the eluate is not over 2 hours old from a generator eluted within the last 24 hours;

- all of the above data in comparison to the CRP data, including the radiolabelling procedure, the amount of radioactivity used for radiolabelling, and the radioactive strength of the final product;
- SOPs for all analytical procedures with associated validation study data;

and

- shipping validation data for the kit covering the furthest distance simulating real-life commercial supply.

5.1.5.5. Stability and packaging

With respect to stability and packaging, the sponsor should provide:

- stability data for 3 consecutive commercial-scale batches, for both real-time and accelerated storage conditions for the drug product (cold kit);
- real-time stability data for 3 consecutive commercial-scale batches for the final radiolabelled drug product;
- study data generated at both upright and inverted orientations for the cold kit and the final radiolabelled drug product;

and

- comparative data to the CRP to support the recommended shelf-life that reflects study conditions and duration, for both:
    - the drug product (cold kit);

    and
    - the final radiolabelled drug product.

Packaging should follow all applicable standards for the product type.

Labelling must follow the regulatory requirements referenced in Section 6.3 - Key legal references.

5.1.5.6. Pharmaceutical comparability and equivalency

With respect to the demonstration of radiopharmaceutical comparability or equivalency of the drug product and the CRP, the sponsor should provide:

- formulation comparability data;
- specifications comparability data for the drug product;
- manufacturing comparability data for the drug product;
- stability and storage conditions data for the drug substance, drug product (cold kit), and final radiolabelled product;
- packaging materials data, including vial and stoppers, for the drug substance, drug product (cold kit), and kit accessories such as radionuclide vial, buffer vial, saline vial, empty (reaction) vial, labels and syringes;

and

- animal biodistribution studies data that help characterize the physicochemical comparability between the drug and the CRP, including studies that may not be truly comparative with the CRP e.g., biodistribution characterization data in a corresponding USP monograph.

5.2. NON-CLINICAL SUBMISSION DATA

Although the focus of the ANDS is on physicochemical comparability, Health Canada may request non-clinical data supplementary to the ANDS requirements set out in the *Food and Drug Regulations*. In this case, the sponsor should provide supplementary approaches alternate to clinical information in order to support or validate claims of equivalence.

If the pharmacopoeial standard chosen for use includes an animal biodistribution element, the sponsor may cross-reference that pharmacopoeial standard with quality data components.

5.2.1. Pharmacology

5.2.1.1. Primary pharmacodynamics

This section exists for CTA and NDS only, and is not applicable to ANDS.

5.2.1.2. Secondary pharmacodynamics

This section exists for CTA and only, and is not applicable to ANDS.

5.2.1.3. Safety pharmacology

This section exists for CTA and NDS only, and is not applicable to ANDS.

5.2.2. Pharmacokinetics

This section exists for CTA and NDS only, and is not applicable to ANDS.

5.2.2.1. Analytical methods and validation

This section exists for CTA and NDS only, and is not applicable to ANDS.

5.2.2.2. Absorption, distribution, metabolism, excretion

This section exists for CTA and NDS only, and is not applicable to ANDS.

5.2.3. Radiation dosimetry

This section exists for CTA and NDS only, and is not applicable to ANDS.

5.2.3.1. Biodistribution, corroborating data, assumptions, and models

This section exists for CTA and NDS only, and is not applicable to ANDS.

5.2.3.2. Summary of radiation dose estimates

This section exists for CTA and NDS only, and is not applicable to ANDS.

5.2.3.3. Presentation of data

This section exists for Clinical CTA and Clinical NDS only, and is not applicable to ANDS.

5.2.4. Toxicology

This section exists for CTA and NDS only, and is not applicable to ANDS.

5.2.4.1. Single-dose acute toxicity studies

This section exists for CTA and NDS only, and is not applicable to ANDS.

5.2.4.2. Repeat-dose studies

This section exists for CTA and NDS only, and is not applicable to ANDS.

5.2.4.3. Genotoxicity and mutagenicity

This section exists for CTA and NDS only, and is not applicable to ANDS.

5.2.4.4. Carcinogenicity

This section exists for CTA and NDS only, and is not applicable to ANDS.

5.2.4.5. Reproductive and developmental toxicities

This section exists for CTA and NDS only, and is not applicable to ANDS.

5.2.4.6. Other information

This section exists for CTA and NDS only, and is not applicable to ANDS.

5.3. CLINICAL SUBMISSION DATA

Although not required, supplementary clinical data can be used to validate claims of equivalence to a Canadian Reference Product (CRP), and to support the safety and effectiveness of the drug product in an ANDS submission.

Clinical submission data is outlined in this Guidance document based on the clinical use of the Schedule C drug.

There are 2 types of Schedule C drugs with respect to clinical submission data: diagnostics and therapeutics.

- Diagnostic radiopharmaceuticals are used to diagnose, monitor, or determine the stage of a disease or condition. Clinical treatment platforms are structured for these specific clinical indications, therefore many standardized principles and guidelines for clinical study design, conduct, data processing and analysis apply to diagnostic radiopharmaceuticals.
- Therapeutic radiopharmaceuticals are used to treat or manage a disease or condition. The drug development cascade and clinical platforms and expectations for other therapeutic drug products (i.e., pharmaceuticals or biologics) typically apply to therapeutic radiopharmaceuticals.

All information in the Clinical subsections apply to both diagnostic and therapeutic radiopharmaceuticals unless otherwise indicated.

If supplementary clinical data is intended to be filed in an ANDS, refer to the NDS Clinical section of the Guidance, where details on the expectations for clinical data are outlined. In such cases, sponsors are also encouraged to consult Health Canada before filing the ANDS.

5.3.1. Pharmacodynamics and pharmacology

5.3.1.1. Primary pharmacodynamics

This section exists for CTA and NDS only, and is not applicable to ANDS.

5.3.1.2. Secondary pharmacodynamics

This section exists for CTA and NDS only, and is not applicable to ANDS.

5.3.1.3. Pharmacology

This section exists for CTA and NDS only, and is not applicable to ANDS.

5.3.2. Pharmacokinetics

5.3.2.1. Analytical methods and validation

This section exists for CTA and NDS only, and is not applicable to ANDS.

5.3.2.2. Absorption, distribution, metabolism, excretion

This section exists for CTA and NDS only, and is not applicable to ANDS.

5.3.3. Radiation dosimetry

With respect to radiation absorbed dose estimates, the sponsor should provide:

- the radiation absorbed dose estimates from the most recent version of the authorized PM of the CRP; or alternatively, the sponsor should provide more recent dosimetry data (e.g., from a publicly available standard such as the ICRP), a rationale for the updated dosimetry data, and the references for the new dosimetry data;

and

- an explanation for the difference in PM content between the product and that of the CRP to be included in the draft PM for the product.

5.3.3.1. Biodistribution, corroborating data, assumptions, and models

This section exists for CTA and NDS only, and is not applicable to ANDS.

5.3.3.2. Summary of radiation dose estimates

This section exists for CTA and NDS only, and is not applicable to ANDS.

5.3.3.3. Presentation of data

This section exists for CTA and NDS only, and is not applicable to ANDS.

5.3.4. Safety and efficacy studies

Supplementary clinical data can be used to validate claims of equivalence to a CRP, and to support the safety and effectiveness of the drug product.

Where human data is available, the sponsor should provide, in consideration with physicochemical comparability, one or both of the following:

- clinical data that supports or validates claims of equivalence;
- clinical data that characterizes efficacy and safety e.g., actual use data.

If the specific case were to arise where Health Canada requests clinical trial data in order to establish or validate claims of equivalence, the sponsor should provide:

- relevant information that characterizes efficacy as per discussions with Health Canada on the evidence being requested e.g., data demonstrating sensitivity, specificity, and estimates for uses of the drug product;
- actual-use data e.g., product specific safety data or supportive efficacy data;
- a comprehensive literature review of the drug product which can include the CRP;

and

- other approaches alternate to supplementary clinical information, discussed in advance with Health Canada.

5.3.4.1. Pivotal trials

This section exists for NDS only, and is not applicable to CTA nor ANDS.

5.3.4.2. Non-pivotal trials

This section exists for NDS only, and is not applicable to CTA nor ANDS.

5.3.4.3. Other clinical studies

This section exists for NDS only, and is not applicable to CTA nor ANDS.

5.3.4.4. Other information

This section exists for NDS only, and is not applicable to CTA nor ANDS.

5.3.5. Biostatistics

If a clinical trial were to be conducted in support of an ANDS or if deemed required under specific circumstances, then please consult the NDS section for Biostatistics information.

6. APPENDIX A – REFERENCES, TEMPLATES, CONTACT INFORMATION, GLOSSARY

Note: References in Appendix A are deliberately not linked to URLs. Sponsors should search on the web for these documents using the documents' titles.

The reality of Government of Canada websites is that URLs change frequently and without warning. This instantly voids the relevance of the link and would result in this Guidance document being quickly and unnecessarily out-of-date. To mitigate this, the Guidance lists titles of documents, without URLs, so that the user can web search for the relevant words in the title, which are less likely to change through time. In this way, this Guidance document will remain up-to-date for longer.

6.1. KEY HEALTH CANADA GUIDANCES

Sponsors should refer to the following key Health Canada Guidance documents. This list is provided as a starting point to help sponsors, and is not exhaustive. It starts with general guidance then is listed alphabetically by topic.

6.1.1. General

Schedule C drugs are subject to the same Guidance documents as are other drugs with respect to general subjects like general submission requirements, Common Technical Document (CTD) format, patents, Notice of Compliance with conditions (NOC/c), priority review, and third party data:

- Guidance for Industry: Management of Drug Submissions
- Guidance Document: Preparation of Drug Regulatory Activities in the Common Technical Document (CTD) Format
- Draft Guidance for Industry: Preparation of Comparative Bioavailability Information for Drug Submissions in the CTD Format
- Guidance Document: Preparation of Drug Regulatory Activities in the Electronic Common Technical Document (eCTD) Format
- Guidance Document: Preparation of Drug Regulatory Activities in the "Non-eCTD Electronic-Only" Format
- Guidance Document: Patented Medicines (Notice of Compliance) Regulations
- Guidance Document: Notice of Compliance with Conditions (NOC/c)
- Guidance Document for Industry: Priority Review of Drug Submissions
- Guidance Document: Drug Submissions Relying on Third-Party Data (Literature and Market Experience)

6.1.2. Adverse drug reaction reporting

Schedule C drugs are subject to the same Guidance documents as are other drugs with respect to adverse drug reaction reporting:

- Reporting Adverse Reactions to Marketed Health Products - Guidance Document for Industry
- Preparing and Submitting Summary Reports for Marketed Drugs and Natural Health Products - Guidance Document for Industry

6.1.3. Basic research

PERs used for basic research are subject to the following Guidance document:

- Guidance Document: A Guide for the Preparation of Applications for Authorization of Positron-emitting Radiopharmaceuticals for Use in Basic Clinical Research Studies

6.1.4. Clinical Trial Applications (CTA)

Schedule C drugs are subject to the same Guidance document as are other drugs with respect to CTAs:

- Guidance Document for Clinical Trial Sponsors: Clinical Trial Applications

6.1.5. Drug Identification Numbers (DIN)

All Schedule C drugs are required to have DINs. Currently, manufacturers of an approved Schedule C drug without a DIN must apply for one in accordance with the following Guidance:

- Guidance Document: Drug Identification Numbers for Schedule C Drugs (Radiopharmaceuticals and Kits)

6.1.6. Drug Establishment Licences (DEL)

Schedule C drugs are subject to the same Guidance documents as are other drugs with respect to DELs:

- Guidance on Drug Establishment Licences and Associated Fees (GUI-0002)
- Drug Establishment Licence Application: Forms and Instructions (FRM-0033)

6.1.7. Drug Submission Fees

Schedule C drugs are subject to the same Guidance document as are other drugs with respect to fees:

- Guidance Document: Fees for the Review of Drug Submissions and Applications

6.1.8. Good Manufacturing Practices (GMP)

Schedule C drugs are subject to the same Guidance documents as are other drugs with respect to GMP:

- Good manufacturing practices guide for drug products (GUI-0001)
- Good Manufacturing practices for active pharmaceutical ingredients (GUI-0104)
- How to demonstrate foreign building compliance with drug good manufacturing practices (GUI-0080)
- Annex 13 to the Current Edition of the Good Manufacturing Practices Guidelines - Drugs Used in Clinical Trials (GUI-0036)

Additionally, there are some Guidance documents that describe GMP requirements specific to Schedule C drugs:

- Annex 3A to the Current Edition of the Good Manufacturing Practices Guidelines - Schedule C Drugs (GUI-0026)
- Annex 3B to the Good manufacturing practices guide for drug products – Positron-emitting radiopharmaceuticals (GUI-0071)

6.1.9. Investigator's Brochure (IB)

Schedule C drugs are like other drugs where an IB should be submitted with the CTA. The IB should provide quality, non-clinical, and clinical information to the investigator. The IB should contain information set out in Section 6.4.3 – References in Appendix A (Section 6.1.9.).

6.1.10. Labelling

Schedule C drugs are subject to the same Guidance documents as are other drugs with respect to labelling:

- Guidance Document: Product Monograph
- Guidance Document - Questions and Answers: Plain Language Labelling Regulations
- Good Label and Package Practices Guide for Prescription Drugs
- Guidance Document for Industry - Review of Drug Brand Names

Additionally,

- Schedule C drugs are subject to the specific labelling requirements in Division 3 of the *Food and Drug Regulations* (see Section 6.3.2 - Canada's *Food and Drug Regulations* in this document).

- Schedule C drugs are subject to a specific Product Monograph template - Product Monograph Template - Schedule C

Finally, for CTA labelling please refer to Section 6.1.4 - Clinical Trial Applications (CTA) in this document.

6.1.11. Master File

Schedule C drugs are subject to the same Guidance document as are other drugs with respect to master files:

- Guidance Document: Master Files (MFs) - Procedures and Administrative Requirements

6.1.12. Post-market - Summary reporting, Risk Management Plan (RMP), Notification of foreign actions

Schedule C drugs are subject to the same Guidance documents as are other drugs with respect to the preparation and submission of Summary Reports for Marketed Drugs. These reports can be presented in several formats, including the Periodic Safety Update Report (PSUR), and the Periodic Benefit-Risk Evaluation Report (PBRER). Risk Management Plans (RMPs) present an additional format for the post-authorization review of drugs.

- Preparing and Submitting Summary Reports for Marketed Drugs and Natural Health Products - Guidance Document for Industry
- Guidance Document - Submission of Risk Management Plans and Follow-up Commitments
- Notifying Health Canada of Foreign Actions – Guidance Document for Industry

6.1.13. Post-market - Post-Notice of Compliance (NOC) Changes

Schedule C drugs are subject to the same Guidance documents as are other drugs with respect to Post-Notice of Compliance (NOC) changes:

- Guidance Document - Post-Notice of Compliance (NOC) Changes: Framework Document
- Guidance Document - Post-Notice of Compliance (NOC) Changes: Safety and Efficacy Document
- Guidance Document - Post-Notice of Compliance (NOC) Changes: Quality Document (Appendix 4 for Schedule C drugs)

6.1.14. Risk Communications

Schedule C drugs are subject to the same Guidance document as are other drugs with respect to risk communications:

- Guidance Document for Industry - Issuance of Health Professional Communications and Public Communications by Market Authorization Holders

A single, streamlined template replaces multiple current templates used to communicate the same information, specifically the Dear Healthcare Professional Letter, the Public Communication, and the Notice to Hospitals:

- Standardized Health Product Risk Communication Template
- Guide for using the Standardized Health Product Risk Communication Template

6.1.15. Specific to Clinical submission data

Schedule C drugs are subject to the same Guidance documents as are other drugs with respect to Clinical-specific submission data:

- Guidance Document: Conduct and Analysis of Comparative Bioavailability Studies
- Guidance Document - Comparative Bioavailability Standards: Formulations Used for Systemic Effects
- Guidance Document - Non-Clinical Laboratory Study Data Supporting Drug Product Applications and Submissions: Adherence to Good Laboratory Practice

6.1.16. Specific to Quality submission data

Schedule C drugs are subject to a different Guidance document than other drugs with respect to Quality-specific submission data for the Quality Information Summary (QIS) and the Certified Product Information Document (CPID):

- Draft Guidance for Industry: Preparation of the Quality Information for Radiopharmaceuticals (Schedule C Drugs) Using the Quality Information Summary-Radiopharmaceuticals (QIS-R) and Certified Product Information Document- Radiopharmaceuticals (CPID-R) Templates

6.2. KEY HEALTH CANADA TEMPLATES

Quality summary templates are available upon request from the Office of Regulatory Affairs (ORA) as per the contact information in Section 6.5.1.2 - Drug submissions:

- QIS-R: Quality Information Summary – Radiopharmaceuticals
- QIS-PER: Quality Information Summary – Positron Emitting Radiopharmaceuticals

- CPID-R: Certified Product Information Document – Radiopharmaceuticals

6.3. KEY LEGAL REFERENCES

Schedule C drugs are subject to the same regulations for submission requirements as other drugs.

The specific regulations for Schedule C drugs, which take into account the unique and distinct manner of these drugs' mode of action, is Division 3 in Part C of the *Food and Drug Regulations*.

6.3.1. Canada's *Food and Drugs Act*

Schedule C in the *Food and Drugs Act* sets out the drugs subject to this Guidance document. To see Schedule C:

- Go to the Website for the Department of Justice, Government of Canada
- Go to Laws, go to Consolidated Acts, search for *Food and Drugs Act*
- Go to Schedule C

6.3.2. Canada's *Food and Drug Regulations*

Schedule C drugs are subject to the *Food and Drug Regulations*, specifically Part C, Divisions 1, 1A, 2, 3, 4, 5, 8. To see the regulations:

- Go to the Website for the Department of Justice, Government of Canada
- Go to Regulations, go to Consolidated Regulations, search for *Food and Drug Regulations*
- Go to Part C, Divisions 1, 1A, 2, 3, 4, 5, 8

6.4. NON-HEALTH CANADA REFERENCES

6.4.1. References in CTA and NDS Non-clinical – Toxicology (Sections 3.2.4.2. and 4.2.4.2., respectively)

6.4.1.1. World Health Organisation (WHO)

- Handbook: Good Laboratory Practice (GLP)

6.4.2. References in CTA and NDS Clinical – Biostatistics (Sections 3.3.5. and 4.3.5., respectively)

6.4.2.1. International Conference on Harmonisation (ICH)

1. E10: Choice of Control Group and Related Issues in Clinical Trials
2. E9: Statistical Principles for Clinical Trials

6.4.2.2. United States Food and Drug Administration (FDA)

- Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics - Guidance for Industry

6.4.3. References in Appendix A (Section 6.1.9.)

6.4.3.1. International Conference on Harmonisation (ICH)

- Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2)

6.5. CONTACT INFORMATION

Please note that the contact information is correct at the time of writing, and may change over time.

6.5.1. For Health Canada enquiries

Enquiries regarding this Guidance document should be communicated to the following areas in Health Canada.

6.5.1.1. Adverse drug reaction reporting

Canada Vigilance Program
Health Products Surveillance and Epidemiology Bureau
Marketed Health Products Directorate (MHPD)
Health Products and Food Branch
Health Canada
Address Locator 1908C
Ottawa, Ontario
K1A 0K9
Canada

Enquiries:

- E-mail: hc.canada.vigilance.sc@canada.ca
- Telephone: 613-957-0337
- Fax: 613-957-0335
- Teletypewriter (TTY): 1-800-465-7735 (help for persons who have a hearing or speech impairment)

To report an adverse reaction:

- Telephone: 1-866-234-2345 (toll-free)
- Fax: 1-866-678-6789 (toll-free)

6.5.1.2. Drug submissions

Office of Regulatory Affairs
Biologics and Genetic Therapies Directorate (BGTD)
Health Products and Food Branch
Health Canada
100 Eglantine Driveway
Address Locator 0601C
Tunney's Pasture
Ottawa, Ontario
K1A 0K9
Canada

Enquiries:

- Email: hc.bgtd.ora.sc@canada.ca
- Telephone: 613-957-1722
- Fax: 613-946-9520
- Teletypewriter (TTY): 1-800-465-7735 (help for persons who have a hearing or speech impairment)

6.5.1.3. Good manufacturing practices (GMP) inspections and Drug establishment licences (DEL)

Generic email accounts have been set up by the Regulatory Operations and Enforcement Branch (ROEB) to provide subject specific guidance. These generic email accounts are regularly monitored by trained and knowledgeable staff.

Please send questions to the following generic email accounts based on the subject.

- ***General enquiries:*** hc.del.questions-leppp.sc@canada.ca
- ***Fee-related enquiries:*** hc.criu_ufrc.sc@canada.ca
- ***API-related enquiries:*** hc.api.questions-ipa.sc@canada.ca
- ***Foreign building GMP enquiries:*** hc.foreign.site-etranger.sc@canada.ca
- ***General GMP enquiries:*** hc.drug.gmp.questions-bpf.medicaments.sc@canada.ca

6.5.1.4. Questions or comments on this Guidance

Office of Policy and International Collaboration
Biologics and Genetic Therapies Directorate (BGTD)
Health Products and Food Branch
Health Canada
100 Eglantine Driveway
Address Locator 0601B
Tunney's Pasture
Ottawa, Ontario

K1A 0K9
Canada

Enquiries:

- E-mail: hc.bgtd.opic-bpci.dpbtg.sc@canada.ca
- Telephone: 613-952-9639
- Fax: 613-952-5364
- Teletypewriter (TTY): 1-800-465-7735 (help for persons who have a hearing or speech impairment)

6.5.2. For non-Health Canada enquiries

6.5.2.1. Canadian Nuclear Safety Commission

Canadian Nuclear Safety Commission
280 Slater Street, P.O. Box 1046, Station B
Ottawa, Ontario
K1P 5S9
Canada

Enquiries:

- Email: cnsc.info.ccsn@canada.ca
- Telephone: 613-995-5894 or 1-800-668-5284 (toll free in Canada and the U.S.)
- Fax: 613-995-5086

6.5.2.2. Oversight of Schedule C drugs in Canada

Health Canada (HC) and the Canadian Nuclear Safety Commission (CNSC) have different responsibilities with respect to the regulatory oversight of Schedule C drugs in Canada.

HC regulates the approval of Schedule C drugs based on satisfactory evaluation of safety, efficacy, and quality of Schedule C drug submissions.

CNSC regulates the radiation safety aspect of Schedule C drugs with respect to the handling, shipping, packaging, transportation, import, export, storage, and disposal of radioactive materials. CNSC also regulates equipment that produces radionuclides for use in the preparation of Schedule C drugs, such as nuclear reactors, medical linear accelerators, and cyclotrons.

6.6. DEFINITIONS

- ***Accelerator*** *(Accélérateur)* = A device to accelerate energetic charged particles linearly or in circular paths by means of a radiofrequency field and an

electromagnetic field in case of cyclotrons. The accelerated particles cause nuclear reactions in the atoms of targets placed in their path. (from Health Canada's *Annex 3B to the Good manufacturing practices guide for drug products – Positron-emitting radiopharmaceuticals (GUI-0071)*)

- ***Automated Synthesis Unit*** *(Module de synthèse automatisée)*, also known as Radiosynthesizer Unit *(Unité de radiosynthèse)* = A closed-system device for the synthesis of radioactive drug substances used in the manufacturing of PERs. The system may be controlled by graphical computer software programs. (see the definition of Radiosynthesizer Unit (RSU) from Health Canada's *Annex 3B to the Good manufacturing practices guide for drug products – Positron-emitting radiopharmaceuticals (GUI-0071)*)
- ***Batch*** *(Lot de fabrication)* = A defined quantity of final product produced in one production run often expressed either in mass (mg or g) or volume (mL or L) or total radioactivity (Ci or GBq), total number of vials or doses. (from Health Canada's *Annex 3B to the Good manufacturing practices guide for drug products – Positron-emitting radiopharmaceuticals (GUI-0071)*)
- ***Bioequivalence*** *(Bioéquivalence)* = A high degree of similarity in the bioavailabilities of two pharmaceutical products (of the same galenic form) from the same molar dose, that are unlikely to produce clinically relevant differences in therapeutic effects, or adverse effects, or both. (from Health Canada's *Draft Guidance for Industry: Preparation of Comparative Bioavailability Information for Drug Submissions in the CTD Format*)
- ***Canadian Reference Product*** *(Produit de référence canadien)* =

  (a) a drug in respect of which a notice of compliance is issued under section C.08.004 or C.08.004.01 and which is marketed in Canada by the innovator of the drug,

  (b) a drug, acceptable to the Minister, that can be used for the purpose of demonstrating bioequivalence on the basis of pharmaceutical and, where applicable, bioavailability characteristics, where a drug in respect of which a notice of compliance has been issued under section C.08.004 or C.08.004.01 cannot be used for that purpose because it is no longer marketed in Canada,

  or

  (c) a drug, acceptable to the Minister, that can be used for the purpose of demonstrating bioequivalence on the basis of pharmaceutical and, where applicable, bioavailability characteristics, in comparison to a drug referred to in paragraph (a)

(from Section C.08.001.1 of the *Food and Drug Regulations* and Health Canada's *Draft Guidance for Industry: Preparation of Comparative Bioavailability Information for Drug Submissions in the CTD Format*)

- ***Effective half-life*** *(Demi-vie effective)* = The time required for a radionuclide deposited in the body to decrease to one-half of its initial quantity as a result of the combined action of radioactive decay and biological elimination. (from the Glossary in the Canadian Nuclear Safety Commission's *RD-58: Thyroid Screening for Radioiodine*)
- ***Gold standard*** *(Étalon-or)* = see Standard of truth

- ***Kit*** *(Trousse)* = A package that is intended to be used in the preparation of radiopharmaceuticals and that
  (a) contains one or more separately packaged units of a drug, other than a radionuclide; and
  (b) may contain empty vials or other accessory items.

(from Section C.03.205 of the *Food and Drug Regulations*)

- ***Ligand*** *(Ligand)* **=** A ligand is an ion or molecule that binds to a radioactive atom such as Tc-99m, In-111, or F-18 to form a final drug product.
- ***Manifold*** *(Manifold)* = A unit for connecting a cylindrical pipe fitting, having a number of lateral outlets, for connecting one pipe with several others used in the Radiosynthesizer Unit. (from Health Canada's *Annex 3B to the Good manufacturing practices guide for drug products – Positron-emitting radiopharmaceuticals (GUI-0071)*)
- ***Manufacture*** *(Fabrication)* = All operations including purchase of materials and products, production, quality control, release, storage, distribution and related controls. (from Health Canada's *Annex 3B to the Good manufacturing practices guide for drug products – Positron-emitting radiopharmaceuticals (GUI-0071)*)
- ***Pharmaceutical equivalence*** *(Équivalence pharmaceutique)* = For a drug referred to in Schedule C of the *Food and Drugs Act*, "pharmaceutical equivalent" is a new drug that, in comparison with another drug, contains identical amounts of the identical medicinal ingredients, in comparable dosage forms, but that does not necessarily contain the same non-medicinal ingredients. (from Section C.08.001.1 of the *Food and Drug Regulations* and Health Canada's *Draft Guidance for Industry: Preparation of Comparative Bioavailability Information for Drug Submissions in the CTD Format*)
- ***QT = Q wave and T wave*** *(onde Q et onde T)* = Measurement through an electrocardiogram (ECG) of 2 of 5 electrical impulses or heart waves – the Q wave and T wave.
- ***Radiopharmaceutical*** *(Radiopharmaceutique)* = A drug that exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons. *(from Section C.03.201 of the Food and Drug Regulations)*
- ***Raw material*** *(Matière première)* = Any substance other than packaging material or an in-process drug that is intended for use in drug manufacture, including substances that appear in the master formula but not in the drug, such as solvents and processing aids. (from Health Canada's *Good manufacturing practices guide for drug products (GUI-0001)*)
- ***Schedule C drug*** *(Médicament de l'annexe C)* = Schedule C drugs are radiopharmaceuticals (including radionuclide generators), and drugs other than radionuclides (kits and components of kits) that are used to prepare radiopharmaceuticals.
- ***Standard of truth*** *(Norme de vérité)* = The standard of truth, or gold standard, is considered to be an independent method used to identify the true disease state, or for measuring the same variable being assessed and measured by a diagnostic radiopharmaceutical, and is regarded as known, or highly considered, to give the true status of the disease state or the true value of the measurement.

- ***Starting material*** *(Matière de départ)* = Any substance entering a production facility for use in the production of a drug product. (from Health Canada's *Annex 3B to the Good manufacturing practices guide for drug products – Positron-emitting radiopharmaceuticals (GUI-0071)*)
- ***Target material*** *(Matière cible)* = A chemical substance which is bombarded with nuclear particles to produce a desired radionuclide. (from Health Canada's *Annex 3B to the Good manufacturing practices guide for drug products – Positron-emitting radiopharmaceuticals (GUI-0071)*)

7. APPENDIX B – OVERVIEW COMPARISON OF CTA-NDS-ANDS

TABLE 2: Which Quality Submission Data Apply to CTA, NDS, and ANDS?

NDS #	Quality	CTA	NDS	ANDS
4.1.1.	GERs	✓	✓	✓
4.1.1.1.	Source	✓	✓	✓
4.1.1.2.	Drug substance synthesis and purification	✓	✓	✓
4.1.1.3.	Radionuclide source and production	✓	✓	✓
4.1.1.4.	Development pharmaceutics	✓	✓	
4.1.1.5.	Formulation and drug product manufacturing	✓	✓	✓
4.1.1.6.	Stability and packaging	✓	✓	✓
4.1.1.7.	Pharmaceutical comparability and equivalency			✓
4.1.2.	PERs	✓	✓	✓
4.1.2.1.	Source	✓	✓	✓
4.1.2.2.	Precursor, ligand, or drug substance source and synthesis	✓	✓	✓
4.1.2.3.	Radionuclide source and production	✓	✓	✓
4.1.2.4.	Development pharmaceutics	✓	✓	
4.1.2.5.	Formulation and drug product manufacturing	✓	✓	✓
4.1.2.6.	Stability and packaging	✓	✓	✓
4.1.2.7.	Pharmaceutical comparability and equivalency			✓
4.1.3.	NGNP	✓	✓	✓
4.1.3.1.	Source	✓	✓	✓
4.1.3.2.	Drug substance synthesis and purification	✓	✓	✓
4.1.3.3.	Radionuclide source and production	✓	✓	✓
4.1.3.4.	Development pharmaceutics	✓	✓	
4.1.3.5.	Formulation and drug product manufacturing	✓	✓	✓
4.1.3.6.	Stability and packaging	✓	✓	✓
4.1.3.7.	Pharmaceutical comparability and equivalency			✓
4.1.4.	Generators	✓	✓	✓
4.1.4.1.	Source	✓	✓	✓
4.1.4.2.	Parent radionuclide and processing	✓	✓	✓
4.1.4.3.	Development pharmaceutics	✓	✓	
4.1.4.4.	Formulation and generator manufacturing process	✓	✓	✓
4.1.4.5.	Stability and packaging	✓	✓	✓
4.1.4.6.	Pharmaceutical comparability and equivalency			✓
4.1.5.	Kits	✓	✓	✓
4.1.5.1.	Source	✓	✓	✓
4.1.5.2.	Drug substance synthesis and purification	✓	✓	✓
4.1.5.3.	Development pharmaceutics	✓	✓	
4.1.5.4.	Formulation and drug product manufacturing	✓	✓	✓
4.1.5.5.	Stability and packaging	✓	✓	✓
4.1.5.6.	Pharmaceutical comparability and equivalency			✓

TABLE 3: Which Non-clinical Submission Data Apply to CTA, NDS, and ANDS?

NDS #	Non-clinical	CTA	NDS	ANDS
4.2.1.	Pharmacology	✓	✓	
4.2.1.1.	Primary pharmacodynamics	✓	✓	
4.2.1.2.	Secondary pharmacodynamics	✓	✓	
4.2.1.3.	Safety pharmacology	✓	✓	
4.2.2.	Pharmacokinetics	✓	✓	
4.2.2.1.	Analytical methods and validation	✓	✓	
4.2.2.2.	Absorption, distribution, metabolism, excretion	✓	✓	
4.2.3.	Radiation dosimetry	✓	✓	
4.2.3.1.	Biodistribution, corroborating data, assumptions, and models	✓	✓	
4.2.3.2.	Summary of radiation dose estimates	✓	✓	
4.2.3.3.	Presentation of data	✓	✓	
4.2.4.	Toxicology	✓	✓	
4.2.4.1.	Single-dose acute toxicity studies	✓	✓	
4.2.4.2.	Repeat-dose studies	✓	✓	
4.2.4.3.	Genotoxicity and mutagenicity	✓	✓	
4.2.4.4.	Carcinogenicity	✓	✓	
4.2.4.5.	Reproductive and developmental toxicities	✓	✓	
4.2.4.6.	Other information	✓	✓	

TABLE 4: Which Clinical Submission Data Apply to CTA, NDS, and ANDS?

NDS #	Clinical	CTA	NDS	ANDS
4.3.1.	Pharmacodynamics and pharmacology			
4.3.1.1.	Primary pharmacodynamics	✓	✓	
4.3.1.2.	Secondary pharmacodynamics	✓	✓	
4.3.1.3.	Pharmacology	✓	✓	
4.3.2.	Pharmacokinetics			
4.3.2.1.	Analytical methods and validation	✓	✓	
4.3.2.2.	Absorption, distribution, metabolism, excretion	✓	✓	
4.3.3.	Radiation dosimetry	✓	✓	✓
4.3.3.1.	Biodistribution, corroborating data, assumptions, and models	✓	✓	
4.3.3.2.	Summary of radiation dose estimates	✓	✓	
4.3.3.3.	Presentation of data	✓	✓	
4.3.4.	Safety and efficacy studies	✓	✓	✓
4.3.4.1.	Pivotal trials		✓	
4.3.4.2.	Non-pivotal trials		✓	
4.3.4.3.	Other clinical studies		✓	
4.3.4.4.	Other information		✓	
4.3.5.	Biostatistics	✓	✓	✓