Draft Guidance for Industry, Preparation of the Quality Information for Radiopharmaceuticals (Schedule C Drugs) using the Quality Information Summary-Radiopharmaceuticals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

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Draft Guidance for Industry, Preparation of the Quality Information for Radiopharmaceuticals (Schedule C Drugs) using the Quality Information Summary-Radiopharmaceuticals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- Radiopharmceuticals (CPID-R) Templates (PDF Version, 65 kb)

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FOREWORD

Guidance documents are meant to provide assistance to industry and health care professionals on how to comply with the policies and governing statutes and regulations. They also serve to provide review and compliance guidance to staff, thereby ensuring that mandates are implemented in a fair, consistent and effective manner.

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 scientific justification. Alternate approaches should be discussed in advance with the relevant program 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 guidance, in order to allow the Department to adequately assess the safety, efficacy or quality of a therapeutic product. 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 guidances.

1. INTRODUCTION

1.1 Purpose

The purpose of this guideline is to provide sponsors of New Drug Submissions (NDSs) and related submissions (responses to information requests during the review, Responses to Notices of Deficiency or Non-Compliance (NODs/NONs), Supplemental New Drug Submissions (SNDSs), and Notifiable Changes (NCs)including Clinical Trial Applications (CTA) with approaches that acceptably meet the regulatory requirements that apply to the "Quality" (chemistry and manufacturing) portions of submissions. Although the approach recommended by the guideline is not mandatory and a different approach may be taken, the sponsor is

encouraged to discuss significant variations with Biologics and Genetic Therapies Directorate (BGTD) in advance to avoid rejection of the submission.

This guideline applies to submissions filed for Schedule C drugs.

The guideline interprets the general requirements given in Section C.08.002(2) (a) to (f) and (l), (m), and (n) and Division 3 of the Food and Drug Regulations, and should be considered authoritative regarding the format for presenting data in New Drug Submissions. The Biologics and Genetic Therapies Directorate (BGTD)recognizes that the guideline cannot cover every possible situation and that specific requirements for a drug depend on the properties of the drug substance, the dosage form and whether the drug is a radiopharmaceutical, kit or generator. However, the guideline has been prepared in as much detail as possible to provide the maximum assistance to the radiopharmaceutical industry.

1.2 Template Requirements

In 1995, the Therapeutic Products Directorate (formerly the Drugs Directorate) implemented a requirement to submit a summary of the quality data included in a submission, called the Comprehensive Summary (Chemistry and Manufacturing) [CS(CM)]. At this time, the Certified Product Information Document (CPID) was also introduced.

1.2.1 Quality Information Summary (QIS) Template

The Quality Information Summary (QIS) Template is intended to replace the Comprehensive Summary (Chemistry and Manufacturing)[CS(CM)] which was required in all drug submissions.

1.2.2 Certified Product Information Document (CPID)

The Certified Product Information Document (required for New Drug and Supplemental New Drug Submissions), compiled by sponsors and issued with the Product Monograph is considered as a part of the Notice

of Compliance package and captures essential technical information related to the drug product.

1.3 Filing Requirements

For general information on filing a Radiopharmaceutical (Schedule C) Drug Submission with the Biologics and Genetic Therapies Directorate (BGTD), the guideline Preparation of Human New Drug Submissions and the Guidelines for the Preparation of Drugs Submissions For Schedule C Drugs should be consulted. Only information specific to the Quality portion (Chemistry and Manufacturing) of the submission is discussed in this Guideline.

1.3.1 Electronic Format

Sponsors must submit electronic files in the following format:

- WordPerfect for Windows, version 8
- Hewlett Packard (HP) Laserjet III or IV printer driver
- IBM compatible
- Univers (Scalable) printer (hard) font.

Sponsors may author the Quality Information Summary (QIS) Template and the Certified Product Information Document (CPID) Template in a different environment(software).However, this software must be compatible with the systems being used by the Biologics and Genetic Therapies Directorate (BGTD).

1.3.2 Submission Format

Quality information (Chemistry and Manufacturing) included in the submission volumes of a Radiopharmaceutical Drug Submission may be organized in a different format than the Template document format. Formats prescribed by a different regulatory agency are now considered acceptable.

1.4 Subsequent Information/Submissions

1.4.1 Responses to Information Requests

During the course of the review of a Radiopharmaceutical Drug Submission, the Biologics and Genetic Therapies Directorate (BGTD) may contact the sponsor by fax to request additional information. As well, a Notice of Deficiency (NOD) or a Notice of Non-Compliance (NON)or a Notice of Non-Satisfactory Letter (NOL)may be issued at the end of the review (see Management of Submissions Policy).

Sponsors are not required to provide a revised version of the completed Quality Information Summary-Radiopharmaceuticals (QIS-R)when filing responses to comments raised by the Directorate unless the magnitude of submission deficiencies warrants the filing of replacement submission volumes.

1.4.2 New Drug Submissions (NDS)

The Quality Information Summary-Radiopharmaceuticals (QIS-R)for a New Drug Submission should be prepared using the entire portion of the QIS-R template, only when the Drug Substance of the final Drug Product is a synthetic chemical entity. However, if the Drug Substance is a biological entity such as monoclonal antibody, rDNA, Blood products, etc., then the relevant portions of the Drug Substance part (Section S) of the Quality Information Summary - Biologicals (QIS-B) Template should completed.

1.4.3 Supplemental New Drug Submissions (S/NDS)

The Quality Information Summary -Radiopharmaceuticals (QIS-R)for a Supplemental New Drug Submission should be prepared using the relevant portions of the QIS-R template. The use of Section S (Drug

Substance) of the QIS-R depends entirely on the nature of the Drug Substance such as Chemical or Biological, according to the principle explained above (1.4.2).

1.4.4 Notifiable Changes (NCs)

Sponsors are not required to provide a Quality Information Summary-Radiopharmaceuticals (QIS-R)when filing Notifiable Changes, unless the change is significant.

1.4.5 Clinical Trial Applications (CTA; commonly known as IND)

Sponsors are encouraged to use the QIS-R template for the preparation of the CTA submissions. It is recommended that as much as possible (available) relevant Quality (Chemistry and Manufacturing)information with regard to the CTA submission must be provided according to the QIS-R template.

2. QUALITY DATA REQUIREMENTS

The data requirements are divided into information that should be provided in the Quality Information Summary-Radiopharmaceuticals (QIS-R), and information that should be provided in the submission. The following subsections are intended to provide a further explanation of the information required in the Quality Information Summary-Radiopharmaceuticals (QIS-R)and are numbered according to the template format.

In certain circumstances, the amount of detail provided in the Quality Information Summary-Radiopharmaceuticals (QIS-R)Template is considered satisfactory, no further information in the submission is required. It is then permissible to omit these subsections from the submission.

G. General Information

In this Section, Sponsors are not required to have a corresponding section in the submission or to make reference to sections of the submission. Information to be included by the Biologics and Genetic Therapies Directorate (BGTD) is shaded. All areas which are not shaded should be completed by the sponsor.

G.1 Submission Summary

This section provides an overview of the submission.

Brand Name:
The brand name under which the product will be marketed and/or used in the Clinical Trial in Canada.

Proper or Common Name:
The proper or common name of the drug substance, as defined by the regulations.

Code Name/No.:
Any research codes used for the drug substance which may appear in information provided in the submission.

Submission Sponsor:
The manufacturer or correspondent acting on behalf of the manufacturer.

Contact and Phone/Fax number:
The person to whom correspondence will be directed.

Drug Classification:
The class of the drug: diagnostic or therapeutic.

How Supplied:
The unit size, volume, activity, calibration time and package sizes, as applicable.

Route(s) of Administration:
The route of administration e.g., intravenous, oral, etc.

Type of Submission:

The type of submission, as defined by the Management of Drug Submissions Policy. Original submissions should be easily differentiated from responses to information requests (e.g., "NDS" versus "NDS: Response to clarifax" versus "NDS: Response to Notice of Non-Compliance").

Date Submitted/Volume(s) Cross Referenced:
The date of the covering letter which accompanies the submission on filing, and the volume numbers which are referenced in the Quality Information Summary (QIS-R) Template.

G.2 Drug Summary

This section provides an overview of the drug described in the submission.

Chemical Name:
New Active Substance (NAS) or Subsequent Market Entry (SME)

Provide the chemical nomenclature followed by "NAS" or "SME"

Pharmacopoeia Status:
Indicate the Pharmacopoeia status of the drug substance and drug product. Both Schedule B pharmacopoeia (e.g., USP, BP, EP) and other pharmacopoeia (e.g., Japanese, German) should be examined. In addition, publications containing proposed pharmacopoeia monographs and changes to existing pharmacopoeia monographs should be examined (e.g., Pharmacopoeia Forum, Pharmeuropeia).

The description should be as complete as possible (e.g. "Drug substance: USP 23 Supplement 4 and BP 1993 Addendum 1996; Drug product: Pharmacopoeia Forum, etc.).

Where appropriate a copy or translation of the pharmacopoeia reference must be appended.

Recommended Dose:
Indicate the dose range for the radioactive (mCi or MBq) dosage form (also applicable for kits) and specify the indication if there are several

different dose/indication combinations.

Packaging Description:
Indicate how the product is packaged (e.g. vial, stopper, aluminum crimp seal, 5-vial pack, etc.)

Expiration Period:
Indicate the expiry time after fabrication. In the case of kits, the expiry of the kit both before and after reconstitution should be stated.

Labelled Storage Conditions:
Indicate the recommended storage conditions. In the case of kits, the storage conditions for the kit both before and after reconstitution should be stated.

Prior Related Submission(s):
List the name and file number of any previously filed submissions which relate to the current submission. This list should include both submissions which are referred to in the current filing for essential information, and those which have not been cross- referenced but would provide assistance in the review process.

G.3 Review Summary

This section is to be completed by the Biologics and Genetic Therapies Directorate (BGTD). Sponsors should not write in this section.

S. Drug Substance

Some of the information required under this section of the Drug Submission may not be available from the sponsor of the Drug Submission (if the Sponsor does not fabricate the Drug Substance). In this case, the supplier of the Drug Substance may file a Drug Master File (formerly Product Master File) directly with Biologics and Genetic Therapies Directorate. This master file will be held in strict confidence and used in support of the new drug only upon the written authorization

("letter of authorization") from the supplier. The above is also applicable for certain radionuclides (not approved for sale in Canada)such as ^{90}Y, ^{188}Re, ^{18}F, ^{13}N, ^{15}O, ^{11}C, etc.

Regardless of whether a Drug Master File is cross-referenced, the sponsor should be able to provide most of the required information on the drug substance, except possibly information in subsections S.2.2 through S.2.4 (see below). It is the responsibility of the sponsor to obtain all other information from the supplier of the drug substance and include this information in the submission. In addition, the submission sponsor is responsible for ensuring that acceptable specifications and properly validated test methods for the drug substance are developed, and also for providing the results of batch analyses performed by the company responsible for routine release testing of the drug substance.

For further information on requirements for Drug Master Files, the Biologics and Genetic Therapies Directorate (BGTD) guideline Drug Master Files should be referred to.

NOTE: For ***well characterized drug substances (old drug substances)*** in new drug products, submit only sections S.3.1 and S.3.2; delete all other drug substance sections.

For ***all radionuclides*** submit S.1.1, S.1.3(a), S.1.4, S.2.1, S.2.2, S.2.3, S.2.4, S.3.1, S.3.2, S.3.3, S.3.4, S.3.5, S.3.6 and S.4

S.1 Nomenclature and Characterization

S.1.1 Nomenclature

(a) Chemical name(s):

Indicate the chemical name(s) of the drug substance, and specify the source of the name(s) (e.g., Chemical Abstracts or IUPAC). Where several chemical names exist, indicate the preferred name.

(b) Laboratory code(s):

Indicate any research codes used for the drug substance which may appear in the submission.

(c) Chemical Abstracts Service (CAS) registry number:
Indicate the number if available, or indicate - not available.

(d) Other name(s):
Indicate any other name(s) by which the drug substance is known.

S.1.2 Structure

(a) Structural formula (including absolute configuration):
Provide the structure of the drug substance which demonstrates its absolute configuration.

(b) Molecular formula and weight:
Provide the molecular formula and weight of the drug substance. For salts, the weight of the free base should also be provided.

(c) Other drugs of similar structure:
For both new active substances and subsequent market entry products, provide the proper or common name and structural formula of similar drugs.

S.1.3 Physicochemical Characteristics

NOTE: Where applicable, details of any studies performed, including test method descriptions, should be provided. Scans or spectra obtained in polymorphic investigations should be provided.

(a) Physical characteristics:
Provide a description of the drug substance, including its appearance, colour, and physical state. For solid forms, indicate whether the drug is crystalline or amorphous.

Melting point, specific gravity, and specific rotation information may also be provided here.

For radionuclides provide the radiation characteristics including decay scheme, emissions, energy and half-life information.

(b) Solubilities:

Provide the solubility of the drug substance in common solvents and those used in production. If descriptive phrases are used (e.g., "sparingly soluble", "slightly soluble") indicate the source of the definitions of these phrases (e.g., USP).

(c) Aqueous pH solubility profile:

Provide the solubility of the drug substance over the physiological pH range.

(d) Polymorphism:

Summarize any studies conducted to determine if the drug substance exists in more than one crystalline form. Indicate the solvent(s) used for recrystallization and the method(s) used to investigate polymorphism. If more than one form exists, describe the differences in physicochemical properties and provide a rationale for the use of the preferred form. In addition, confirm that this form is the same as that used in clinical and bioavailability studies.

(e) Particle size distribution:

Summarize any particle size studies performed on the drug substance, especially for batches used in recent or pivotal clinical trials and/or comparative bioavailability studies. This applies only to those situations where particles (colloid, microaggregates or macroaggregates, or spheres) are involved. Indicate the source of the drug substance, the batch numbers, and the use of the batches by the sponsor. Indicate the method of analysis, and results.

A graphical presentation of results, demonstrating the full distribution is preferred. (Cumulative percent frequency results, highlighting the 10th, 50th, and 90th percentile should be captured in tabular form. If this information exceeds 1 page, it should be appended.

(f) pKa and pH values:

Provide the pKa(s) and pH values of the drug substance.

(g) UV maxima and extinction coefficient:

Indicate the UV maxima and extinction coefficient of the drug substance.

(h) Other:
Where relevant, provide information on the partition coefficient, solvate formation, tautomers, etc.

(i) Source of above information:
Indicate whether the above information was generated by the company responsible for routine release testing or a third party, or obtained from a reference text or literature reference. Where applicable, indicate the production site and grade (i.e., production batch or reference standard) of the drug substance.

S.1.4 Radionuclidic and Radiochemical Properties

Radionuclidic purity and impurity:
Summarize studies performed to elucidate and quantitate the radionuclidic purity and impurity. Append radiation spectra where appropriate.

Radiochemical purity and impurity:
Summarize studies performed to illustrate and quantitate radiochemical purity and impurity. Append applicable HPLC, ITCL, etc. reports.

Source of the above information:
Indicate whether the above information was generated by the company responsible for routine release testing or a third party.
Where applicable, indicate the production site and grade (i.e., production batch or reference standard) of the drug substance.

S.1.5 Elucidation of Chemical Structure

NOTE: Where appropriate, elemental analysis is normally required as confirmation of structure, in addition to ultraviolet, infrared, nuclear magnetic resonance, and mass spectra. Copies of the actual spectra with assignments should be provided.

Details of any studies conducted on isomers should be provided.

Type of studies conducted which provide evidence of chemical structure:

Provide a list of the studies of the techniques performed to elucidate or confirm the structure of the drug substance (e.g., elemental analysis, NMR, IR, UV, MS). Do not provide a discussion of the results.

Potential isomerism:
Where relevant, describe stereoisomers which may result from the method of manufacture, and identify the steps where they may be produced. If the drug is to be marketed as a single isomer or a fixed ratio of isomers, provide the rationale for this decision. For subsequent market entry products, include a summary of any comparative studies performed.

Source of above information:
Indicate whether the above information was generated by the company responsible for routine release testing or a third party, or obtained from a reference text or literature reference. Where applicable, indicate the production site and grade (i.e., production batch or reference standard) of the drug substance used.

S.2 Fabrication

S.2.1 Fabricator(s)

(a) Name and address of all facilities involved in production of drug substance:

Provide the name and address of all companies involved in all aspects of drug substance production. If certain companies are responsible only for specific steps, this should be indicated.

If a Drug Master File (DMF) **filed with the Biologics and Genetic Therapies Directorate (BGTD)** is cross-referenced, provide the **Directorate assigned** DMF number. Confirm that a letter of authorization, and indicate the location of the letter in the submission.

S.2.2 Quality Control of Starting Materials

NOTE: The drug submission should contain the following information:

- A full list of the articles used in the manufacture of the drug substance/radionuclide should be provided. This list should include all of the ingredients used in the synthesis, isolation, and purification steps, regardless of whether they undergo any change or are eliminated or removed during the process. In case of radionuclide produced by cyclotron, the list should also include the name and source of the target material used in the production. These articles or substances should be identified by established names or complete chemical names.
- Specifications for all materials including target materials (if any) used in the manufacturing of the drug substance/radionuclide such as identity, purity, and potency, where applicable - should be provided. Rigid specifications, including tight control of potential impurities, is expected for starting material used in an one-step synthesis. Special consideration should be given to potential isomeric impurities in the starting material, as such contaminants could be carried through the synthesis to the final product.
- Full specifications for isolated intermediates should also be provided.

(a) Purity test specifications for starting materials:
Provide the purity tests and limits only for starting materials, as well as the location in the submission of the full specifications for these compounds.

(b) Specifications for other starting materials may be found in Volume/Page:
Provide the location in the submission of the full specifications for other compounds used in the manufacture (e.g. reagents, solvents, etc.).

S.2.3 Description of Synthesis/Fabrication

A complete description of all manufacturing steps should be provided. This information should include typical reaction conditions such as time, temperature, and catalysts. Names and amounts of substances and percent yields for each step should be included. Reaction steps which have low yields should be discussed.

For radionuclides include the nuclear reaction involved for the production of the desired radioisotope such as 18O(p,n)18F, etc.

A detailed description of the isolation and purification of the drug substance is also required. If the drug substance is prepared sterile, a complete description of the method used to sterilize each batch should be provided.

For subsequent market entry products, a comparison with any published route(s) of synthesis should be provided where available.

(a) Method of fabrication flow sheet:
Provide a flow sheet which includes all steps of the synthesis or process conducted within corporate facilities (i.e., starting from commercially available or well-characterized starting materials). Starting materials/targets/reactants, reagents (including catalysts), and **all** solvents used in each step should be indicated. Names and structures of all starting materials and intermediates (whether isolated or not) should be included.

Flow sheets that exceed one page should be appended to the summary (e.g. in the case of a lengthy synthesis or where several production routes are presented as a consequence of multiple proposed sources of drug substance supply).

(b) Description of fabrication steps:
Describe key steps of the manufacturing method, including a brief explanation of the specificity of reactions or processes used to obtain a desired isomer, and any isolation steps.

The description of purification steps should include all solvents used. Drying time and temperature should be indicated.

(c) Alternate methods or variations:
Describe any potential alternate methods or variations (e.g., those used by a different production site or if an intermediate does not meet an in-process control limit).

Note: This information could, alternatively, be included in (a) or (b) above. In this case, include a reference statement (e.g., "See (a), above").

S.2.4 In-Process Controls

Note: Provide a brief rationale for any unique in-process control tests or limits.

Provide a brief description of the in-process controls used to monitor the fabrication, such as completion of individual reaction steps (e.g., Step 3: HPLC, NLT 95%).

Note: This information could, alternatively, be included in S.2.2 above. In this case, include a reference statement (e.g., "See S.2.3(b), above").

S.3 Control Tests on the Drug Substance

S.3.1 Specifications

A copy of the actual specifications used by the company responsible for routine release testing should be provided.

Specifications that will ensure batch-to-batch uniformity must be developed based on the data obtained during development. The major regulatory and industry concern is to reproduce, for marketing, a drug substance of a quality equal or superior to that used in the toxicological, pharmacological, and clinical testing. To assure this reproducibility, the specifications for the drug substance must ensure:

a. unequivocal identification
b. strict control of impurities, and

c. control of physical characteristics such as crystalline structure and particle size if these have been shown to affect the stability.

Although the specifications developed depend on the nature of the drug substance, these would normally include physical characteristics, identity, purity, and potency. The physical characteristics might include such properties as appearance, odour, particle size distribution, or X-ray diffraction pattern.

One of the most important functions of the specifications is to unequivocally identify the drug substance. If the drug substance is composed of more than one moiety, then each moiety should be specifically identified (e.g., in the case of a hydrochloric acid salt, both the base and the salt should be identified). In the interests of cost and science, it is desirable to use a single test or only that combination of identity tests that will unequivocally identify the drug substance. The use of several identity tests, which specifically identify the drug substance only when taken together, is not encouraged. The infra-red spectrum should be included in the specifications for all drug substances, whenever practical and meaningful.

Purity tests - such as loss on drying, residue on ignition, specific rotation, and heavy metal content should be included, depending on the synthetic route or nature of the drug substance. In all cases, a test or tests for possible contaminants or impurities having structures related to the drug substance must be included. This test should ensure that all batches of the drug substance meet the same criteria of purity as those batches used in the toxicological, pharmacological, and clinical testing. It is normally expected that individual unidentified impurities be limited to less than 0.1%.

Most specifications include an assay procedure with its limits. HPLC is recommended whenever feasible. A non-specific assay method would be considered acceptable if the identity test is specific and the impurities

are rigidly controlled.

In case of radionuclides (cyclotron or reactor produced), decay characteristics must be explained by means of decay schema. In case of generators, nuclear reaction should be indicated along with the half-life of both the parent and daughter radionuclide. Radionuclidic purity assay should be performed for all of the above cases, and the assay

method must be validated. All the radioactive and non-radioactive impurities must be characterized. Any uncharacterized impurities (radioactive or non-radioactive) must be limited to a lowest possible limit; if a higher amount is allowed that must be scientifically justified.

Provide the specifications by completing all sections of the specifications Table provided.

"Method Type/Code/Source" should be described, for example, as "HPLC/XG-324-01/House". The test method revision number should be included under "Code", regardless of whether it is part of the official code for the method. The appropriate pharmacopoeia should be cited under "Source" when a general method in the pharmacopoeia is followed (e.g., loss on drying), regardless of whether a monograph exists for the drug.

S.3.2 Justification of Specifications

a. Justification for unique tests/limits (other than impurity limits):

   Provide a summary of the reasons for implementing certain unique tests or limits. Such tests and limits may include particle size, loss on drying/moisture content, stannous content, wide range of pH or a 90% or less than 90% radionuclidic/radiochemical purity, etc.

b. ustification for impurity limits should be discussed under S.3.4, below.

S.3.3 Test Methods and Validation

Note: Copies of the actual test methods used to test the drug substance should be provided. The raw data generated in the validation study should also be provided. For a CTA (IND) submission validation study is an optional requirement, and should be provided if the study data is available.

Sponsors are encouraged to consult the guideline Acceptable Methods for assistance with method validation.

Test methods and validation may be found in Appendix numbers:

Provide the Appendix reference where all test methods and accompanying validations are located. Do not provide actual test methods or validation data in this section.

Generally, only methods such as UV, TLC, HPLC, and GC need to be described in the Appendices. The test method and validation data should be used for this purpose. The Tables should be used without revision, except in cases where there are several impurities. In this case, additional rows may be added to existing Tables in order to encompass additional impurities.

If there are other unique tests which the sponsor feels should be described in the summary, a Table may be developed by the sponsor for this purpose.

S.3.4 Impurities and their Qualification

(a) **Potential** drug related impurities (starting materials, intermediates, by-products, degradation products):

Provide a description of the potential drug related impurities by completing all sections of the impurities Table provided. All potential impurities should be described, regardless of whether they have been

detected in any batches. The Table may be expanded to include more rows as necessary. If the Table expands beyond one page, the impurities Table should be appended to this document.

For impurities which appear in the manufacturing flow sheet of the drug substance, the code name and chemical or common name should be consistent with those appearing in the flow sheet. The structure should show the absolute configuration, where applicable. The origin should be as detailed as possible (e.g., by-product formed in step 3 of the synthesis). It should be indicated whether the impurity is also a metabolite in humans.

(b) **Potential** process-related impurities (residual solvents, reagents):

Provide a list of the residual solvents and reagents which may potentially remain in the drug substance. The source of these elements should be obvious from the fabrication flow sheet of the drug substance.

(c) **Actual** drug substance purity:

Provide a summary of the purity of several batches of the drug substance.

i. *Test method(s) used and summary of method and validation if different than those described in S.3.1:*

   If any batches were tested by a method different than the method currently used to quantify impurities and described in the specifications, the differences should be outlined. If the differences could potentially affect the accuracy or precision of the method, a summary of the validation should be provided.

ii. *Actual impurity levels detected (including quantities found in toxicological/clinical study batches) by the company responsible for routine testing of the drug substance:*

Provide a summary of the impurities detected by completing all sections of the impurity results Table provided.

Where feasible, the results of impurity analysis should be provided for all batches included in the submission. The actual levels of all impurities found should be reported rather than vague statements such as "within limits" or "conforms". In cases where a large number of batches have been produced, it is acceptable to specify the total number of batches analyzed and provide a range of results. Results may be categorized, if appropriate, to emphasize an event or a change (e.g. higher levels of impurities in earlier batches prior to refinement of the process and/or the purification method). If numerous trace impurities (i.e. < 0.1% each) are present, it is sufficient in the summary to report their total level and number. Toxic and named impurities present at > 0.1% should be reported separately.

(d) Discussion of values close to or outside of current limits:

In the event of a specification change, discuss impurities (if any) that have been close to or outside of the current specifications limits.

(e) Justification for proposed limits:

Similar to the (d)above scenario, change of the specifications for the impurities must be justified.

S.3.5 Reference Standard

Note: This section applies to radionuclide reference standards. Complete for the non-radioactive drug substance if applicable.

a) Source of reference standard used in analysis in the submission.

b) Source of reference standard for use in routine post market substance and drug product testing. Reference point (a), if applicable.

c) Certificate of analysis for the reference standard may be found in Volume/Page.

If a house reference standard is used, complete the following:

d) Information on the house reference standard

i. Method of preparation (fabrication)

ii. Specifications

iii. Summary of calibration of the house reference against primary standard, or qualification of the house reference standard if an accepted reference standard is not available.

S.3.6 Batch Analysis

1. Information on all drug substance batches described in the submission.
   Complete the Table provided. The term "use" refers to the end use of the substance, for example: pre-clinical studies, clinical trial, toxicology, etc.
2. Confirmation that the batch analysis results reported in the submission were generated by the company responsible for routine testing of the drug substance.
3. Description of incomplete analysis if any tests described in S.3.1 were not conducted.
4. Summary of any changes in specifications (test methods/limits and validation where appropriate) and a rationale for those changes over the production history.
5. Discussion of results which are close to or outside of current limits.

S.4 Container/Closure

Description of container(s)/closure(s) and labelling:

This section should include such pertinent information as on the importance of desiccants, absence of oxygen and container preparation intended to avoid adsorption of the substance on the glass or plastic surface, etc.

S.5 Stability

S.5.1 Stability Data

Note: This section does not apply to radionuclides.

a. Stress studies (conditions/parameters/results).

b. Long term (real-time) and accelerated stability studies:

i. Stability study information:
Complete the Table provided.

ii. List of study test parameters.

iii. Test methods used and summary of method(s) and validation if different than those described in S.3.1:

iv. Description of incomplete analyses if any tests described above were not conducted.

v. Discussion of results.

S.5.2 Stability Conclusions

Note: This does not apply to radionuclides.
Proposed storage conditions (including warnings) and duration permitted before retesting and/or proposed expiration period:
The conclusion stated in this section must be substantiated by data presented in section S.5.1.

P. Drug Product

P.1 Development Pharmaceutics

a. Role of all ingredients in the formulation (excluding drug substance):

   Complete the Table provided.

b. Rationale for choice of formulation and process (including packaging, where applicable):

c. This should include not only on the rationale for the choice of ingredients but also rationale for the quantity of each ingredient.

d. Information on batches used in in-vitro studies (characterization, comparison, etc.):

   Provide detailed studies (comparison of chemical, radiochemical purity/impurity, stability, physicochemical and biological properties, etc.)carried out with various batches during formulation development. This should also include information regarding deviation or modification of formulation used for pre-clinical/clinical/toxicological studies.

e. Discussion of impact of formulation changes on the safety and/or efficacy of the product:

   Discuss if and how any safety or efficacy factor was compromised due to formulation modification.

f. Summary of in-vitro characterization studies (applicable for the final dosage form such as radiopharmaceutical and/or radiolabelled kit stability and vial/stopper compatibility studies):

The studies should include the following:

i. Adsorption of the drug by the container and closure(vial and rubber septum/stopper)

ii. Stability of the drug when stored in an inverted vial in contact with the rubber septum/stopper.

iii. If applicable, radiolabelling a kit using 99mTc pertechnetate with a 72 hour in growth of 99Tc (from a generator which has not been eluted for 72 hours).

iv. If applicable, effect of radiolabelling a kit using 99m Tc pertechnetate eluate of more than 2 hours old).

v. The effect of radiolabelling a kit (as applicable) with 99mTc eluate or other radionuclides eg. 111In (approved in Canada) obtained from a variety of sources.

vi. The effect of radiolabelling a kit with various amounts (minimum and maximum) radioactivity and volume.

P.2 Fabrication

P.2.1 Activities:

(a) BGTD assigned DMF number, subject matter, and confirmation that an appropriate letter of authorization has been provided for any aspects of production or component formulation described in a cross-referenced Drug Master File:
Provide in Tabular form a list of drug master files which have been referenced in the submission. This list should include the DMF number, the subject and a reference to the volume/page of the submission. For each DMF a letter of authorization (addressed to BGTD) must be included in the submission and the volume/page should be provided in this Table.

(b) Name, address, and most recent GMP rating (including reference date) of all facilities involved in the production of the drug product:

i. Fabricator:

ii. Packager:

iii. Labeller:

iv. Tester/testing sites (components and drug product):
For each tester/testing site named, indicate the test being performed.

v. Post-market stability tester/testing site (drug product):
For each tester/testing site named, indicate the test being performed.

vi. Importer:

vii. Distributor:

P.2.2 Fabricating Formulae

(a) For Generators:

Include a detailed description of the radiochemistry of the generator, which should include nuclear reaction (parent to daughter), generator components (column, adsorbent, eluent, sterile filters, collection vial, etc.). Also provide a quantitative list (by weight or radioactivity) of components where applicable.

(b) For Kits and Radiopharmaceuticals:

Provide a quantitative list of all the ingredients present in the kit or in the radiopharmaceutical.

P.2.3 Fabricating Process

Description of manufacturing process (including packaging operations where applicable):
The description should include manufacturing of the commercial batches. However, if clinical/toxicological batches were manufactured by a different method, a brief description of the method must be given here including rational for such modification.

Anticipated range of commercial (production) batch sizes:
Batch size of each production lot must be specified in terms of total lot size (L/kg) and as well number of unit dosage (# of vials/capsules, etc.). Also specify if any batch-to-batch variation is anticipated. Also, where

applicable the radioactivity/drug unit should be stated or the size of the generator (GBq/Ci), with reference to the Calibration Time (CT) or Activity Reference Time (ART).

Manufacturing documents may be found in Volume/Page:
The manufacturing documents should include an actual batch production record (BPR). Note that this is not applicable for CTA submissions.

P.2.4 In-Process Controls

The nature of in-process control required will depend on the type of drug being fabricated. For example, for radiopharmaceuticals containing particulates in-process assessments of particle size would clearly be required. The list below serves as an example, and is not intended to be all inclusive.

a) Generators:

i. Radionuclidic purity of the parent.
ii. Radiochemical purity analysis of the eluate.
iii. Appearance and pH of the eluate
iv. Assay for other contaminants in the eluate.

b) Kits and Radiopharmaceuticals:

i. Chemical and radiochemical purity assay.
ii. Radionuclidic purity analysis.
iii. Appearance (also for reconstituted kits).
iv. pH
v. Weight/volume/radioactivity variation.
vi. Assay of other critical components such as stannous ion, etc.

P.2.5 Validation of the Process:

Processes used in the fabrication of the drug product which can impact in the quality of the drug product must be validated. This would apply for example, steam sterilization and freeze-drying processes. Note that this

not applicable for CTA submissions.

P.3 Control Tests on all Ingredients (excluding drug substance)

1. Confirmation that all ingredients present in the formulation are not prohibited for use in drugs by the Canadian Food and Drug Regulations.
2. Specifications for all ingredients should include purity, identity, appearance, chemical form (free base or salt) expiry and storage, etc.
3. Control tests for all ingredients:

Fill in the Table provided.

P.4 Control Tests on the Drug Product

P.4.1 Specifications:

Specifications and the limits should be sufficiently precise to adequately characterize the drug product or radiopharmaceutical kits which contain a reducing agent, measurement of nitrogen and oxygen in the vial headspace. Also for radiopharmaceuticals and/or Kits regardless of whether it contain a chemical or biological entity the following measurements may be required.

The following tests are only an example and are not all in encompassing.

- Appearance/Clarity/Colour
- pH
- Osmolality
- Quantititive composition of all ingredients
- Radiochemical and radionuclidic purity
- Chemical purity
- Sterility
- pyrogenicity (Bacterial endotoxin)

- Oxygen content
- Nitrogen content
- Particle size distribution
- Biodistribution (if applicable)

P.4.2 Justification of Specifications:

Provide a list of proposed control test methods for each specification criteria and justify the method and specification limit.

P.4.3 Test Methods and Validation

Test methods and validation studies must be given in a numbered Appendix. Note that validation studies are not required for CTA submissions. However, if the study data is available the sponsor may consider to include in the above Appendix.

P.4.4 Batch Analysis:

Complete all the items (a-f) under section P.4.4.

P.5 Container/Closure

P.5.1 Source

Name and address of the Supplier(s) for container/closure.

P.5.2 Description

A detailed description of the container/closure should be provided including Pharmacopoeia references (where applicable).

P.5.3 Composition

A list of materials used in the fabrication of the above container/closure such as elastomeric components, glass vials, etc. should be provided.

P.5.4 Specifications

Provide complete specification in a Tabular format.

P.5.5 Qualification of Container/Closure System

The summary of qualification studies should contain a list of test parameters and their limits.

P.6 Stability

P.6.1 Stability Data

For kits, studies are required for both kit and radiolabelled form of the drug. Stress studies should incorporate criteria which will simulate extremes of temperature during shipping and transportation.

For Kits, Radiopharmaceuticals and Generators study data are required to support the proposed expiry in recommended storage conditions.

Complete the sections in P.6.1(a) or P.6.1(b) as applicable to the present submission.

P.6.2 Stability Conclusions

The study conclusion should be based on the studies given in section(s) P.6.1(a) or P.6.1(b). Also indicate the recommended storage condition(s) for the proposed expiration date or time post calibration.

P.6.3 Post Market Stability Protocol

A detailed description of the protocol must be provided. This should include all the information in section 6.3 (i-iv). Note that this section is not applicable for CTA submissions.

O. Other Information

O.1 Product Monograph or investigators' brochure (for CTA submissions) and Labels

a. Indicate the location (volume/page)for the Product Monograph/Investigators' Brochure provided in the submission.

b. Indicate the file name of the enclosed electronic copy of the Product Monograph/Investigators' Brochure.
c. Indicate the location (volume/page) for the samples of an inner label and an outer label.

O.2 Appendices

Complete the Table (according to the submission type).

O.3 References

a. Indicate the location (volume/page)of the list of references given in the submission.
b. Indicate the location (volume/page) of paper copies of references (if any) attached in the submission.

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