**INTRODUCTION**

Do you wish to receive communications from Health Canada regarding this submission electronically (e.g. via email)?  Yes  No

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| --- | --- |
| **Proposed Product:** | **Canadian Reference Product (CRP):** |
| Brand Name:  Drug Substance(s):  Company Name:  Dosage Form(s):  Strength(s): | Brand Name:  Drug Substance(s):  Company Name:        Dosage Form(s):  Strength(s): |

# MODULE 1 – ADMINISTRATIVE AND PRESCRIBING INFORMATION

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| **Administrative Information** | | |
| **1.2.3** | **Certifications and Attestation Forms**  Does a valid Certificate of Suitability (CEP) issued by the European Directorate for the Quality of Medicines and Healthcare (EDQM) exist for this Active Pharmaceutical Ingredient (API) and manufacturing site/process?  If “Yes”, has the CEP, along with all annexes and attestations been filed in section 1.2.3 according to the Guidance document: [Use of Certificates of Suitability as supporting information in Drug Submissions](https://www.canada.ca/en/health-canada/services/drugs-health-products/public-involvement-consultations/drug-products/draft-guidance-document-use-certificates-suitability-supporting-information-drug-submissions.html)? | Yes  No  Yes  No  Not Applicable |
| **1.2.5** | **Compliance and Site Information**  Have the filing requirements in Health Canada’s February 10, 2017 [*Notice* *Submission Filing Requirements – Good Manufacturing Practices (GMP)/ Drug Establishment Licences (DEL)*](https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/notice-submission-filing-requirements-good-manufacturing-practices-establishment-licences.html)been met, for all activities listed in the Notice?  Comments:  Have all batches included in the submission been manufactured and tested at a Good Manufacturing Practices (GMP) compliant facility?  If No, provide location of discussion: | Yes  No  Yes  No |
| **1.2.6** | Authorization for Sharing Information List Master File (MF) number(s) referenced in the submission:  MF numbers:  Types (i.e. I – IV):  For the above MFs:   1. Have Letters of Access granting access to the MFs on behalf of the submission sponsor been provided? 2. Are the MFs in order and up to date (e.g. fees paid)?   Comments:  If there is no MF referenced, and there is no CEP filed as per section 1.2.3, is all information on the drug substance manufacturing process and controls and the drug product container closure system included in the submission? | Not Applicable  Yes  No  Yes  No  Yes  No  Not Applicable |
| **1.2.7** | **International Information**  Provide information on the product application filing and marketing status (Mkd = Marketed) of the proposed product in the following jurisdictions:  United States Food and Drug Administration (USFDA):  European Union (EU):  If filed in the EU, indicate applicable procedure:  Centralized  De-Centralized  Mutual Recognition  National  Switzerland’s Swissmedic:  Singapore’s Health Sciences Authority (HSA) :  Australia’s Therapeutic Goods Administration (TGA): | Not Applicable  Filed  Mkd  Filed  Mkd  Filed  Mkd  Filed  Mkd  Filed  Mkd |
|  | Has Foreign Review Information for any of the above jurisdictions been provided?  Review reports (specify jurisdiction, if applicable:       )  Other  If Yes, has the [Foreign Review Attestation and Summary of Quality Differences: Subsequent Market Entry Products (Human Drugs](file://C:\Users\HCHERRY\AppData\Local\Microsoft\Windows\Temporary%20Internet%20Files\Content.Outlook\OOZ2QXIG\*%20https:\www.canada.ca\en\health-canada\services\drugs-health-products\drug-products\applications-submissions\guidance-documents\use-foreign-reviews\attestation-summary-quality-differences-subsequent-market-entry-products-human-drugs.html)) been provided? | Yes  No  Not Applicable  Yes  No  Not Applicable |

# MODULE 3 - QUALITY

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| **Drug Substance** | | |
| **S.1** | **General Information**  Does the proposed active pharmaceutical ingredient comply with the interpretation of “Pharmaceutical Equivalent” as per the Food and Drug Regulations, and “Identical Medicinal Ingredient” as described in Health Canada’s policy Interpretation of “Identical Medicinal Ingredient” (2003) and notice Interim Policy on Health Canada's Interpretation of Medicinal Ingredient (2015)? | Yes  No |
| **S.4** | **Control for the Drug Substance**   1. Do any of the proposed limits for impurities exceed the applicable International Council on Harmonisation (ICH) Qualification Threshold in Q3A? 2. If “Yes” to a), specify the basis used for qualifying the impurity limits:   The limits are qualified in an official compendial monograph (specify:      )  The limits are qualified in publicly available scientific literature (specify, and indicate where in the submission this literature is located:      )  Levels of these impurities are observed in the CRP  Limits are based on safety (e.g. toxicological) data (indicate where in the submission the safety studies and discussion are located:      )  Other (specify:      )  Does the submission include a discussion of potential genotoxic impurities (e.g. including the identification of potential structural alerts)?  Location of discussion:  Have analytical results been provided for those batches used in non-clinical, clinical, or comparative bioavailability studies (where applicable), and comparative in vitro and stability studies?  If no, indication location of the justification:  If the scale of the batch is less than 1/10th commercial scale, has a justification of why the smaller scale is representative been provided?  Location of justification:  Have Certificates of analysis been provided for the pivotal batches?  Location of discussion: | Yes  No  Not Applicable  Yes  No  Not Applicable  Yes  No  Yes  No  Not Applicable  Yes  No |
| **S.7** | **Stability**  Has the minimum amount of drug substance stability data (6 months of stability data on at least three pilot scale batches (at least 10% of commercial scale and representative of the commercial process) or two pilot scale batches and one small scale batch (if justified as representative of the commercial process)) been provided as per ICH stability guidances?  If no, provide justification: | Yes  No |

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| **Drug Product** | | | | |
| Proposed strength(s): | | | | |
| Approved strength(s) for the Canadian Reference Product (CRP): | | | | |
| **Batches used in comparative bioavailability or physicochemical study/ studies** | | **Test Product** | **Canadian Reference Product (CRP)** | |
| Strength(s): | |  |  | |
| Batch number(s): | |  |  | |
| Batch size: | |  | Not applicable. | |
| Largest proposed commercial batch size: | |  | Not applicable. | |
| Is/are the size(s) of the batch(es) used in comparative bioavailability or physicochemical studies at least “pilot scale” (i.e. manufactured by a procedure fully representative of and simulating that to be applied to a full production scale batch: for solid oral dosage forms, at a minimum of one-tenth that of full production scale or 100,000 units, whichever is larger, or for liquid dosage forms, at a minimum of one-tenth that of a full production scale or 20 litres, whichever is the larger)?  Yes  No  If No, provide justification: | | | | |
| **P.2** | **Pharmaceutical Development** | | | |
| Has a comparative in vivobioequivalence study been provided on each of the proposed strengths?  If ‘No’ to the above, has a request for waiver to perform the comparative in vivobioequivalence study and justification been provided?  If a waiver is requested, is the product qualitatively and quantitatively the same as the CRP?  If No, discussion is provide in section:  For comparative bioavailability or physicochemical studies, was the reference product sourced from the Canadian market?  If a foreign sourced reference product was used, have criteria outlined in the [Guidance Document: Use of a Foreign-sourced Reference Product as a Canadian Reference Product](https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/canadian-reference-product-guidance.html) been addressed?  Location of results/study:  Was the same lot of the foreign sourced reference product used in the comparative bioavailability studies and/or all in vitro comparative studies?  If No, provide justification: | | | Yes  No  Yes  No  Not applicable  Yes  No  Not applicable  Yes  No  Not Applicable  Yes  No  Not Applicable  Yes  No  Not Applicable |
| **For solid oral dosage forms:**  Have comparative dissolution profiles been provided for all generic strength(s) not used in a comparative bioavailability study against the generic strength for which bioequivalence was demonstrated?  Has justification of the choice of dissolution method including discussion of the discriminatory power of the dissolution method been provided?  Is the generic product identical to the CRP with respect to the scoring configuration?  If No, has a justification been provided as per the criteria listed in the notice [Tablet Scoring of Subsequent-entry Pharmaceutical Products](https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/notice-tablet-scoring-subsequent-entry-pharmaceutical-products.html)?  Location of justification:  If the product is scored, have results of a divisibility study (including dissolution and weight loss) been provided for all scored strengths of the generic product?  Location of results/study: | | | Not a solid oral dosage form  Yes  No  Yes  No  Yes  No  Yes  No  Yes  No  Not scored |
| **For oral solutions**  If a biowaiver is proposed, has justification for biowaiver been provided based on:   1. Comparative physicochemical results between the oral solution of the CRP and this generic in accordance with the [Guidance Pharmaceutical Quality of Aqueous Solutions](https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/chemical-entity-products-quality/notice-guidance-industry-pharmaceutical-quality-aqueous-solutions.html)? 2. Experimental comparative aqueous solubility and intestinal permeability results between the API of the CRP and the API of this generic? 3. Other data   Location of discussion: | | | No biowaiver proposed  Yes  No  Yes  No  Yes  No |
| **For topical dosage forms** (Semi-solids and solutions with penetration enhancers):  Has direct evidence of safety and efficacy, through clinical studies/bio-availability studies/surrogate models (e.g. vasoconstrictor assay for corticosteroids), been provided on each of the proposed strengths?  If ‘No’ to the above has justification for waiver been provided based on the following data:   1. Comparative formulations, physicochemical properties, microstructure and in-vitro release data (for emulsions) 2. Other data   Location of discussion:  Does the formulation include penetration enhancers at a different level to the CRP?  If Yes, discussion is provided in section : | | | Not topical  Yes  No  Yes  No  Yes  No  Yes  No  Not Applicable |
| **For dosage forms with delivery devices:**  Has a comparison of the physical and operating characteristics of the device attributes and performance of the delivery system been provided, between the generic and the CRP? | | | No delivery device  Yes  No |
| **For liquid and semi-solid dosage forms including sterile parenterals and inhalation products:**  Have results of comparisons of the test and reference products been provided (e.g. formulations, physicochemical properties)?  Location of results/ discussion: | | | Not a liquid or semi-solid dosage form  Yes  No |
| **P.2.4** | **Container Closure System**  **For liquids and semi-solid dosage forms:**  Has an assessment of extractable compounds associated with the primary components of the container closure system (CCS) in contact with the drug product been performed in accordance with USP <1663>\*?   1. If yes, extractable study/results provided in section     ? 2. If no, justification provided in section   Has assessment of potential leachable compounds associated with the primary components of the CCS in contact with the drug product performed in accordance with USP <1664>\*?   1. If yes, leachable study/results provided in section: 2. If no, justification provided in section   For elastomeric closures:  Have results been provided for:  USP <381> Elastomeric Closures for Injections (includes USP <87>/<88> tests)\*  If no, justification provided in section  For plastic container closure systems:  Have results been provided for:  USP <661> Containers\*  USP <671> Containers – Performance Testing\*  If no, justification provided in section  Has assessment of the suitability for the plastic containers/ components been performed in accordance with USP <1661>\*?   1. If yes, suitability results for the primary plastic container /components (e.g. bottles/stoppers) of the CCS in contact with the drug product provided in section      ? 2. If no, justification provided in section   Glass containers:  Has assessment of the suitability of the glass containers been performed in accordance with USP <1660>\*?   1. If yes, suitability screening results for the primary glass component of the CCS (e.g. vial) in contact with the drug product provided in section:      ? 2. If no, justification provided in section   \* Or the equivalent General Chapter of the Ph. Eur. | | | Not a liquid or semi-solid dosage form  Yes  No  Yes  No  Not an elastomeric closure  Yes  No  Not a plastic container closure system  Yes  No  Yes  No  Yes  No  Not a glass container  Yes  No |
| **P.2.5** | **Microbiological Attributes**  For products containing antimicrobial preservatives, have the results of a Preservative Effectiveness Study been provided?  If No, provide justification: | | | Product does not require preservative  Yes  No |
| **P.2.6** | **Compatibility**  **For products to be diluted or reconstituted or mixed with other media (e.g., juice) for administration:**  Have in-use stability data been provided for ALL diluents or reconstitution solutions over the concentration range, storage conditions, and storage times as specified in the Product Monograph for the CRP?  If No, provide justification: | | | Product does not require constitution or dilution  Yes  No |
| **P.3.4** | **Controls of Critical Steps and Intermediates**  Are there any high risk aspects of the manufacturing process for this product, as detailed in section P.3.4 of the Quality Guidance Document (e.g. describe unusual features, novel excipients, direct compression processes for low dose drugs, unconventional processes, stability of the API during manufacturing)  If yes, indicate location of discussion: | | | Yes  No |
| **P.3.5** | **Process Validation and/or Evaluation**  Has a process validation report been included with results performed on three consecutive, production-scale batches for each strength of the drug product (and for each fill size for liquid and semi-solid dosage forms)?  If No, indicate for which strengths and fill sizes the report(s) have been provided :  If No, has a process validation protocol been submitted with a commitment that three consecutive, production-scale batches of the drug product will be subjected to prospective validation? | | | Yes  No  Yes  No |
| **For sterile products:**  Has the following documentation been provided:  Drug substance Bacterial Endotoxin test validation  Drug product Bacterial Endotoxin test validation  Validation of filters used for aseptic filtration  Has a determination of extractables and leachables from process equipment (e.g. filters, tubing, coatings) or a commitment and study outline been provided?  If Yes, indicate where report is located (e.g. Membrane Compatibility Test Report, Extractable Substances documentation):  Has the validation of sterilization process been conducted?  For aseptic sterilisation techniques, has a justification been provided for the use of aseptic processes versus terminal sterilization?  If No, provide justification:  Has the validation of sterilization of packaging materials been conducted and the validation report included in the submission?  Has a study on the integrity of the container closure system been included? | | | Not a sterile product  Yes  No  Not applicable  Yes  No  Not applicable  Yes  No  Not applicable  Yes  No  Not applicable  Yes  No  Not aseptically processed  Yes  No  Yes  No  Yes  No |
| **P.5** | **Control for the Drug Product**  Have the release and stability specifications for the drug product been provided?   1. Do any of the proposed limits for impurities exceed the applicable International Conference on Harmonisation (ICH) Qualification Threshold in Q3B? 2. If “Yes” to a), specify the basis used for qualifying the impurity limits:   Limits in an official compendial monograph (specify:      )  Information in publicly available scientific literature (specify:      )  Levels of these impurities observed in the CRP  based on safety (e.g. toxicological) data (if yes, identify sections of Module 4 where complete safety data and justification for the limits have been provided:      )  Other (specify:      )  Has batch analysis been conducted on the number of batches and batch sizes as specified in Quality Guidance Document (i.e. have three batches of each strength been manufactured at a minimum of pilot scale from each proposed commercial manufacturing site)?  If No, provide justification:  For liquids (including lyophilized powders for reconstitution into a solution), if the maximum proposed commercial batch size is less than 20 litres, have the executed batches included in the drug submission been manufactured at the maximum proposed commercial batch size?  Has a Risk Assessment Summary for Elemental Impurities been included (to be in line with ICH Q3D)?  If yes, indicate the location of this document (section P.2/P.5.5/P.5.6/other): | | | Yes  No  Yes  No  Not Applicable  Yes  No  Yes  No  Not Applicable  Yes  No |
| **P.8** | **Stability**  Has the minimum amount of drug product stability data (6 months of stability data on at least three pilot scale batches (at least 10% of commercial scale and representative of the commercial process) or two pilot scale batches and one small scale batch (if justified as representative of the commercial process)) been provided as per ICH stability guidances?  If No, provide justification: | | |  |
| Yes  No |
| Have stability data been provided on at least three unique batches of each strength at pilot scale?  If No, provide justification: | | | Yes  No |
| Have three batches of stability data been provided in all types of container closure systems?  If No, provide justification: | | | Yes  No |
| Have the results of stress testing (e.g. including Photostability studies of the drug product) been provided?  Location of results/study:  If No, provide justification: | | | Yes  No |
| For sterile parenteral liquids, have transportation protocols or transportation study results provided?  If No, provide justification:  For liquids and semi-solid dosage forms packaged in plastic containers, has stability data been provided at low humidity conditions as specified in Quality Guidance Document?  If no, indicate location of justification including calculation for water loss at the reference relative humidity (e.g. using permeation coefficients) as per ICH Q1E: | | | Yes  No  Not Applicable  Yes  No  Not Applicable |
| **Regional Information** | | | | |
| **R.1.1** | **Executed Production Documents**  Have copies of the executed production documents been provided for two batches of each strength (including the test batches used in the pivotal clinical and/or comparative biostudies, or in cases where the strength was not used for a pivotal study, have the executed production documents for the stability batches been provided)?  If No, provide justification:  If the Executed Production Documents have not been provided in English or French, have translations into either English or French been provided?  If multiple drug product manufacturing sites are proposed, has the above been provided for at least one batch from each proposed manufacturing site?  If No, provide justification:        For sterile products, have the primary packaging executed packaging records been provided? | | | Yes  No  Yes  No  Not Applicable  Yes  No  Not Applicable  Not a sterile product  Yes  No |
| **R 1.2** | **Master Production Documents**  Have copies of the drug product master production documents been provided for each proposed strength, commercial batch size, and manufacturing site?  If the Master Production Documents have not been provided in English or French, have translations into either English or French been provided?  For sterile products, have details of manufacturing processes (e.g. washing, treatment, sterilizing, and depyrogenating of containers, closures and equipment; filtration of solutions, final inspection of the product, and sterilization cycle) been provided, including referenced Standard Operating Procedures (SOPs) where applicable?  If No, provide justification: | | | Yes  No  Yes  No  Not Applicable  Not a sterile product  Yes  No |

# MODULE 5 – CLINICAL STUDY REPORTS

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| **Comparative Bioavailability Studies** | |
| Has a Module 5 been provided?  Yes  No  If “No”, leave the below section blank.  **List comparative bioavailability study or studies included in the submission:**  *The description should include study title, study number, study design, products administered, dose and conditions of administration (e.g., 1 x 100 milligrams, fasting/fed).* | |
| For each study – Has justification been provided for the use of non-standard conditions of administration (e.g., fed instead of fasting conditions, modifications to test meal composition for studies conducted under fed conditions)?  Location of justification: | Yes  No  Not Applicable |
| For each study - If the study was conducted outside of Canada, provide a list of clinical and bioanalytical facilities employed:  *The description should include the name and address of each facility.* |  |
| For each study - Has documentation establishing the GCP compliance of the clinical and bioanalytical facilities to current FDA or ICH standards been provided?  Specifically, documentation should be provided to support the outcome(s) of inspection(s) of the sites by the FDA or an ICH Authority. Note that documentation from the FDA should include all 482 and 483 Forms that were issued, the responses to the deficiencies noted on Form 483, as well as the Establishment Inspection Report.  Comment: | Yes  No  Not Applicable |
| **Test Product**  Are all strengths proportionally formulated to the strength administered in the comparative bioavailability study as per the criteria outlined in the Bioequivalence of Proportional Formulations policy?  Is a waiver of the requirement to provide comparative bioavailability data requested?  If “Yes” to the above, justification for the waiver request is based on:  Proportionality Policy?  In-vitro in-vivo correlation based data?  Biopharmaceutics Classification System (BCS)?  Location of results/study:  If “Yes” to the BCS-based waiver:  Is this an immediate-release product?  Have the eligibility criteria been met as listed in the ICH M9 guideline: Biopharmaceutics Classification System-based Biowaivers, Section 3?  Has a completed BCS based biowaiver evaluation [template](https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/templates/biopharmaceutics-classification-system-based-biowaiver.html) been provided?  If No, provide justification: | Yes  No  Not Applicable  Yes  No  Not Applicable  No BCS-based waiver  Yes  No  Yes  No  Yes  No |
| **Reference Product**  Are reference product labels for the lot used in the comparative bioavailability studies provided, including expiry date and lot number? | Yes  No |

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| **Bioanalytical Method** | |
| Analyte(s) measured:  parent  metabolite  Has justification been provided for basing bioequivalence on metabolite data instead of parent?  Location of justification if provided: | Yes  No  Not Applicable |
| Has the bioanalytical report been provided?  Has the method validation report been provided?  Does the validation report include the following stability experiments with multiple (minimum three) replicates at each of the low quality control (QC) and high QC concentrations in the appropriate matrix (including the same anticoagulant used in the comparative bioavailability study), as per Health Canada’s October 8, 2015 *Notice for Industry: Clarification of bioanalytical method validation procedures*?  Long term stability data (frozen at the temperature used in the study) in spiked plasma to cover the maximum storage period for subject samples.  Freeze-thaw stability data for the number of cycles that is considered to be reflective of the number of cycles experienced by subject samples from the study (frozen at - the temperature used in the study and thawed at room temperature) in spiked plasma.  Bench top stability data in spiked plasma over a length of storage that is considered to be reflective of the processing period of the batches of the subject samples from the study  If no, provide location of justification: | Yes  No  Not Applicable  Yes  No  Yes  No |

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| **Sponsor Attestation** | | | |
| *I, the undersigned, certify that:*   1. The information and material included in this checklist is accurate and complete. 2. No information is false or misleading and no omissions have been made that may affect its accuracy and completeness. | | | |
| Name of Authorized Signing Official | Signature | | Date (YYYY/MM/DD) |
| Company Name and Address | | Title | |
| Telephone Number | Fax Number | | E-mail Address |