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Guide to Submitting an Application to INESSS for Medications, Blood Products, and Medical Devices Related to Drug Administration

A publication of the Institut national d'excellence en santé et en services sociaux (INESSS)

Drug and Technology Assessment Directorate for Reimbursement Purposes

Québec

Guide for Submitting an Application to INESSS for Medicines, Blood Products, and Medical Devices Related to Drug Administration

Preamble

This document, drafted and published by the Institut national d'excellence en santé et en services sociaux (INESSS), provides the information manufacturers need to prepare an application for registration or addition—in the case of a blood system product—regarding a health product (innovator drug, generic drug, biosimilar drug, blood system product, and medical device related to drug administration), for the purpose of public reimbursement. The required documents, the terminology used, and the corresponding specifics are presented herein.

It should be noted from the outset that the following categories of health products are not eligible for listing, as they are not covered by the General Drug Insurance Plan (RGAM):

- prescription drugs:
    - for aesthetic or cosmetic purposes;
    - for the treatment of alopecia or baldness, erectile dysfunction, or weight loss;
    - for cachexia or to stimulate appetite.

For other exclusions, please consult the most recent *List of Medications*.

In addition, in order to comply with INESSS guidelines (e.g., previous recommendations) and ministerial decisions, certain health products cannot be evaluated by the Institute, namely:

- dressings:
    - circular or heel dressings;
    - compression bandages;
    - requiring the creation of a new recognized indication;
- therapeutic garments;
- human skin substitutes.

It should also be noted that only natural health products licensed by Health Canada whose common name is already listed or that are marketed in different salt forms may be the subject of a listing application.

For a health product to be listed on the RGAM *Drug List*, the *Institutional Drug List*, added to the *Quebec Blood System Product List*, or reimbursed through another public mechanism (e.g., a specific program), a manufacturer must submit a listing application to INESSS. The submitted application must comply with the content, format, and organization specified in this submission guide.

For information on:

- preparing an application for listing with INESSS;
- the process for submitting a registration application (Form 6 – Multi-source Drugs – Generic or Natural Health Product);
- the process for submitting a registration or addition application (other registration forms);
- the evaluation process;
- the fees associated with the appraisal.

Please visit our website, under the Manufacturers' Appointments section.

For any other questions, please contact the **Drug and Technology Assessment Branch for Reimbursement** by email:

- For drugs, blood products, and medical devices related to drug administration: inscription@inesss.qc.ca
- For generic drugs and natural health products: generique@inesss.qc.ca
- For non-pharmaceutical innovations:itdm@inesss.qc.ca and refer to the evaluation request form and corresponding Submission Guide.

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1 SUBMISSION OF APPLICATIONS FOR LISTING

1.1 Applications submitted in accordance with the requirements of Form 6 (new multi-source drug—generic or natural health product)

All manufacturers of multi-source drugs must submit their applications for registration exclusively through the INESSS online submission portal. The application must comply with the requirements of Form 6. The procedure to follow is available in the "Manufacturers' Corner" section of the website (Signing Up for Electronic Submission of a Registration Application and Electronic Submission of a Registration Application).

1.2 Applications submitted in accordance with the requirements of other fact sheets

INESSS has implemented a secure electronic submission solution using the Ministry of Health and Social Services' (MSSS) secure ShareFile platform. This submission method is available for drug registration applications that meet the requirements outlined in registration forms 1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13, A, B, and C, as well as for blood system products (PSS) and certain drug delivery devices (DM), in accordance with the applicable requirements. Please note that INESSS may, in certain cases, ask you to submit an application through this mechanism (e.g., evaluation of a post-protection drug). Here are some guidelines to follow for submission:

- Please request the secure link in advance, specifying the desired date, by writing to inscription@inesss.qc.ca . Please note that the link provided will be valid for 24 hours;
- Please ensure that you separate the documents into **4 .zip files** according to the different evaluation components (administrative, clinical, economic, others) as described on the registration forms, if applicable;
- Please avoid creating multiple subfolders. An example of a submission folder structure is provided in Appendix VI;
- For the clinical component, **please clearly identify the 5 most relevant studies, publications, or documents** (in accordance with the selections made in the "Summary Description of the Application" form) and rename the files to be submitted by indicating: order of importance, the title of the document (generally the name of the study), the name of the first author, and the year;

  Example:

1. Study Name_First Author's Name_Year
2. Study Name_First Author's Name_Year
3. Etc.

- It is not permitted to embed one document within another via an external link. Each document must be "unique";
- The summary boxes in the clinical section of the "Summary Description of the Dossier" form, tailored to the subject of the evaluation (drug, biosimilar, PSS, or medical device), must be completed by focusing on the 5 studies, publications, or documents identified as most relevant to the evaluation, where applicable. Studies involving one or more relevant active comparators are of particular interest. In the absence of data directly comparing the subject under study with the most relevant comparator(s), at least one indirect comparison, whether published or unpublished, must be submitted and included as one of the 5 relevant studies, publications, or documents selected;
- Provide the *Clinical Study Report (CSR)* for the main clinical studies that have been published or are available as a manuscript for publication, if applicable. Please create a subfolder named "Clinical Study Report";
- If posters or abstracts from conference proceedings are available and only if they are related to the five most relevant publications, whether published or available as manuscripts for publication, please create a subfolder titled "Posters or Abstracts";
- If it is necessary to provide additional publications relevant to the evaluation, in accordance with the requirements outlined in this guide, please create a subfolder titled "Other Publications";
- Documents submitted with your application must, where applicable, include a complete bibliography of the references used.

2 SELECTING THE FORM THAT MATCHES YOUR APPLICATION

You must refer to the following forms to determine the documents required based on the type of application you are submitting.

If more than one form applies to your application, choose the one with the most requirements (usually Form 1).

Please note that for any request, you may provide a written explanation for the absence of a document that does not apply or for which it is impossible to meet the requirements.

File number	Type of request
Initial application for drug evaluation	
Form 1	New drug, new cell therapy, new gene therapy, new advanced therapeutic product, or new radiopharmaceutical or New indication for a drug, cell therapy, gene therapy, advanced therapeutic product, or radiopharmaceutical already listed – With a Health Canada Notice of Compliance
Form 2	New drug, new cell therapy, new gene therapy, new advanced therapeutic product, or new radiopharmaceutical or New indication for an already registered drug, cell therapy, gene therapy, advanced therapeutic product, or radiopharmaceutical – Pending a notice of compliance from Health Canada
Form 3	New combination of drugs that have already been issued a notice of listing – With a notice of compliance from Health Canada
Form 4	New strength or new dosage form of a drug that has already been issued a notice of registration
Form 5	New biosimilar drug or new indication for a biosimilar drug – With a Notice of Compliance from Health Canada
Form 6	New multi-source drug (generic drug or natural health product)
Form 7	New diagnostic agent belonging to an already listed generic name
Form 8	New nutritional formula
Form 9	New form of a diagnostic agent or nutritional formula
Form 10	New dressing belonging to a generic name already listed
Form 11	New format or form of a dressing already registered

Form 12	New biosimilar drug or new indication – Awaiting a Notice of Compliance from Health Canada
Form 13	Request for exemption from the application of the lowest price method (LPM)
Request for re-evaluation of a drug	
Form A	New drug, new cell therapy, new gene therapy, new advanced therapeutic product, or new radiopharmaceutical already listed
Form B	New strength, new presentation, or new dosage form of a drug already listed
Form C	New diagnostic agent or new nutritional formula belonging to a generic name already listed
Application for evaluation or re-evaluation of a blood system product (PSS)	
PSS Form 1	New PSS or new indication for an existing PSS on the List – With a Health Canada Notice of Compliance
PSS Form 2	New PSS or new indication for a PSS already on the List – Pending a Notice of Compliance from Health Canada
PSS Form 3	New strength or new dosage form of a PSS that has already been the subject of a notice of addition to the List
SS Form A	Re-evaluation – New PSS or new indication for a PSS already on the List
PSS Form B	Reevaluation – New strength or new dosage form of a PSS that has already been the subject of a notice of addition to the List
Application for evaluation or re-evaluation of a medical device (MD[1]) related to the administration of a drug	
Medical Device Form 1	New medical device (MD) related to the administration of a drug or a new indication for an MD already on the List – With Health Canada approval
MD Form 2	Revised version of a medical device (MD) related to the administration of a drug that has already been the subject of a Notice of Registration – With Health Canada approval
MD Form A	Re-evaluation – New medical device (MD) related to the administration of a drug or new indication for an MD already on the List
MD Form B	Re-evaluation – Iterative version of a medical device (MD) related to the administration of a drug that has already been the subject of a Notice of Listing

1 MD: medical device or medical instrument as defined by Health Canada

Examples of form selection for specific situations

Specific situation	Form to use
First application	
Biosimilar drug whose generic name has not been evaluated for the intended indication **Post-patent drug**: a drug that has never been evaluated by the Institute, has never been listed for an indication recognized by Health Canada, and for which the patent has expired[1] **Off-label therapeutic product**: a health product licensed in Canada and evaluated for an indication not included in the Canadian product monograph and that is eligible for listing by the Minister[1]	Form 1 or 2
Generic drug whose generic name is not or is no longer listed on the drug lists **Nutritional formula or diagnostic agent** belonging to a generic name not listed on the drug lists **New indication** for a drug already listed on the drug formulary and addition of a **new strength** **New diagnostic agent** with a Drug Identification Number (DIN) **New allergen** whose common name, form, or strength is not listed on the drug lists **Natural health product** whose common name has already been listed on the drug lists	Form 1
Generic drug whose form or strength is not or is no longer listed on the drug lists **New strength** of a drug already listed in the drug lists (e.g., two strengths are indicated on the product monograph, but only one is listed) **New salt for a drug** whose generic name is already listed on the drug lists	Form 4
New strength or new form of a biosimilar drug already listed on the drug lists	Form 5
New strength of a drug listed on the *Drug List – Institutions* (injectable products only)	Form 6
Request for Reevaluation	
Biosimilar drug – reevaluation of a recognized indication	Form A
Biosimilar drug whose generic name has been refused on therapeutic grounds[1]	Form A
Innovative drug – modification of an indication listed on the drug lists	Form A
Innovative drug – monitoring requirement – conditional approval or promising potential/value proposition	Form A
Multi-source drug (generic or natural health product)	Form 6

Specific situation	Form to use
Dressing	Form 10

[1] It is always best to contact INESSS and explain your situation to determine which registration form to use, as different scenarios may arise.

For any questions regarding the choice of a form, please contact the **Drug and Technology Assessment Directorate for Reimbursement Purposes** by email:

- For drugs, blood products, and medical devices related to drug administration:inscription@inesss.qc.ca
- For generic drugs and natural health products: generique@inesss.qc.ca

Special Considerations for Certain Applications

1. Application for evaluation of a drug that must be administered in combination with another product (from another manufacturer, for example) not listed on the drug lists

The manufacturer must indicate in the mandatory advance notice as well as in the cover letter accompanying the application that the drug must be administered in combination with another product not listed on the drug lists. INESSS will contact the manufacturer directly to obtain a "Drug Listing Application" form for that other product. If the product to be administered in combination with the drug under evaluation is already listed on the *Drug List – Institutions o*nly, a "Drug Listing Application" form will be requested to update the product information and validate the institutional sales price.

2. Companion tests

INESSS defines a "companion test" as any biomedical analysis whose results are intended to select a population (based on its status or according to a recognized predictive marker) that could benefit from a specific treatment (targeted therapy), to monitor it, or to anticipate its foreseeable adverse effects. The test is thus considered a "companion" to the treatment.

INESSS also reserves the right to evaluate any other test (e.g., diagnostic test) present in the care pathway and related to the drug under evaluation, where the implications could have consequences for the organization of laboratory services in Quebec should the drug be reimbursed for the recognized indication.

The manufacturer must indicate in the mandatory prior notice whether the health product submitted for listing requires the use of a companion test or not.

To help manufacturers decide whether to submit a companion test evaluation dossier to INESSS, in accordance with applicable procedures, and to expedite the evaluation process, the Institute will contact manufacturers by email within two weeks of receiving the advance notice to inform them of its intention to proceed with or decline to evaluate a test related to the drug, regardless of whether the manufacturer checked the "Companion Test" box on the mandatory advance notice. The information provided to manufacturers would be based on a preliminary analysis conducted by the team responsible for the admissibility of companion tests.

If there is a need to evaluate a test associated with a drug, the manufacturer must provide, if not already done, the Companion Test Evaluation Dossier **at the same time as the drug evaluation dossier is submitted**. Note that an invoice for the evaluation of the drug and the companion test will be issued if the drug dossier is deemed admissible and is activated.

If there is no need to evaluate a test associated with a drug, no Companion Test Evaluation Dossier will be required by INESSS.

Please note that during the evaluation process, the need to evaluate a test associated with a drug may arise, in which case the manufacturer will be notified by email to provide additional information. In such situations, since the dossier is already active, no additional fees will be charged.

When a companion test is required, the drug's budget impact analysis should include the annual number of tests to be performed (screening and confirmatory) as well as their cost. This analysis must also account for the impact of variations in the anticipated number of tests, based on the platforms most likely to be used or implemented in Quebec. If a two-step approach is required (e.g., immunohistochemistry [IHC] confirmed by molecular testing), the cost of the confirmatory test must also be considered. The weighted values listed in the appendices of the MSSS's *Quebec Directory and Measurement System for Medical Laboratory Procedures* can serve as a source of information for estimating these costs. To better understand the companion diagnostic evaluation process, please consult the link Synchronized Companion Diagnostic Evaluation Process. For any other questions regarding companion diagnostics, please contact us by email attestcompagnon@inesss.qc.ca .

3. Agnostic Therapies in Oncology

INESSS defines an agnostic therapy as a therapy that could benefit a population selected based on the status of a predictive marker.

However, the evidence submitted to INESSS is often of low quality and lacks a comparator treatment. In such cases, the submitted data must meet the following criteria, by tumor site:

Admissibility criteria for the evaluation of an agnostic therapy in oncology	
Unmet medical need	• Rare cancer and/or rare pathogenic variant **AND** • Comparative study difficult to conduct **AND** • No treatment available for the intended indication **OR** available treatment options have modest efficacy or high toxicity

Number of patients	• At least 35 patients per tumor site evaluated • Patient data may come from different studies or data sources
Efficacy	For each tumor site to be evaluated: 1 - Objective response rate ≥ 60% **OR** • Objective response rate ≥ 20% **AND** duration of response ≥ 9 months

Relationship between the forms and the preparation of a submission

The data sheets outline the requirements applicable at the time of submitting an evaluation request and indicate the elements that INESSS will accept at a later date as soon as possible.

- A written justification is required for each missing document. INESSS will assess the relevance of this justification during the admissibility review and will notify the manufacturer in writing if the requirement is not met.

Various abbreviations are used in the fact sheets; here are their meanings:

n/a = not applicable;

R = Required as of the date the evaluation request was filed;

RD = Required as soon as possible.

IMPORTANT INFORMATION

Submission of a mandatory notice

The manufacturer must notify INESSS at least two months (60 days) in advance of its intention to submit an application for evaluation. A mandatory notice of intent is required for applications to be submitted in accordance with the requirements of Form 1, 2, 5, 12, or A for a drug, PSS, or MD, as applicable. **INESSS accepts registration applications prior to the announced filing date.** The manufacturer is responsible for notifying INESSS of any changes to the information provided in the advance notice submitted at the time of the official application filing or promptly during the evaluation process.

Submission of Evaluation Applications

An application for registration may be evaluated prior to the issuance of a Notice of Compliance by Health Canada. However, the Notice of Compliance must be expected within the next 180 days.

To better align the timing of INESSS's recommendations with those of the Canadian Drug Agency (CDA-AMC) and to reduce access delays—particularly for negotiations conducted jointly by the provinces—evaluation requests should be submitted simultaneously to both INESSS and CDA-AMC.

Manufacturers are also encouraged to participate in the harmonized review process between Health Canada, INESSS, and the CDA-AMC and to consent to the exchange

of information as early as possible. Such aligned submissions may be considered of paramount importance for the sequencing of evaluation requests, just like priority submissions to Health Canada, including ORBIS projects.

For administrative reasons, particularly those related to billing, the contact information for the Canadian entity responsible for the application and/or the entity that will officially act as the manufacturer recognized by the Minister of Health for registration must be provided to INESSS.

Documents to be submitted in French

Two documents must be submitted in French as part of the application for registration or addition:

- the cover letter;
- the "Application for Registration of a Drug" or "Application for Addition of a PSS" or "Application for Registration of a Medical Device" form.

French translations of other documents are preferred and may be submitted at a later date.

During meetings with INESSS, French is the preferred working language. It is recommended that supporting documents be provided in French.

Submission of Documents Under Review

A manufacturer may submit a registration or addition request (for a PSS) to INESSS only when able to provide all required documents (R) at the time of submission. INESSS's evaluation may begin even if other documents are submitted at a later date (RD).

INESSS may also make additional requests during the evaluation process.

If, during the evaluation, the manufacturer wishes to submit new documents on an exceptional basis (e.g., a new publication, an update to the main clinical study, or a manuscript from a clinical study not included in the file), this must be agreed upon in advance with INESSS, as it is expected th , all information relevant to the evaluation will be submitted from the outset. The use of this information remains at the discretion of INESSS.

Any additional information may result in further delays in the evaluation, as INESSS must consider the stage of the process at which this new information is shared. The information must be submitted to INESSS by requesting a secure electronic submission link or by email toinscription@inesss.qc.ca .

Process for revising the guaranteed selling price (GSP) with manufacturers

Under certain circumstances detailed in the "Procedure for Manufacturers – Revision of the Guaranteed Selling Price (GSP)," INESSS may initiate a review with a manufacturer regarding the GSP submitted in its application for listing. When a revision is accepted by the manufacturer, a new "Application for Drug Registration" form must be submitted.

Images Provided in the Evaluation Request

INESSS may wish to reproduce or adapt images, figures, tables, or photos provided by the manufacturer in its submission for publication in its recommendations. If so, the manufacturer will be notified when the recommendation is sent, and their authorization

will be required prior to publication. If a third party holds the copyright, INESSS will rely on the manufacturer's cooperation to authorize this use.

Final requirements for submitting a recommendation to the Minister

IMPORTANT: It is the manufacturer's responsibility to submit any missing documents related to its application for registration or to inform INESSS of any related delays.

INESSS must have in its possession:

- the Notice of Compliance or the registration certificate issued by Health Canada;
- the official product monograph or user manual in the case of a medical device;
- the final product labels (or confirmation that the draft labels have been approved by Health Canada);

before submitting its recommendation to the Minister of Health.

For a harmonized evaluation project with Health Canada, INESSS, and CDA-AMC, the manufacturer is still responsible for submitting the required documents to INESSS to complete its file.

In addition, the manufacturer must have paid all fees charged by INESSS for the evaluation before the recommendation can be submitted to the Minister.

Please note that no new information will be accepted once the recommendation has been submitted to the Minister of Health.

Procedures related to the issuance of a Notice of Non-Compliance or Insufficiency by Health Canada

In the event that Health Canada issues a Notice of Non-Compliance (NON) or a Notice *of Deficiency* (NOD) for a health product under review, INESSS will suspend its work for a maximum period of six months. It is the manufacturer's responsibility to promptly inform INESSS when the timeline of Health Canada's regulatory process is altered by the issuance of a Notice of Non-Compliance or a Notice of Deficiency. Upon receipt of information regarding the resumption of the review at Health Canada and of the associated documents deemed admissible, the file will be eligible for further review. Work will resume as soon as resources become available. If the information is not provided within this timeframe, the manufacturer must submit a letter of withdrawal of the evaluation application to INESSS and resubmit the application to the Institute in accordance with standard procedures. Please note that a new application may be submitted to INESSS if the notice of compliance is expected within the next 180 days. Fees are non-refundable even if the manufacturer withdraws their application during the evaluation process.

Procedures for Issuing a Recommendation with a Follow-Up Condition

In the event of a recommendation with a follow-up condition, the manufacturer may, without waiting for a request from INESSS, submit a request for re-evaluation at any time, in accordance with standard procedures. INESSS may also request that the manufacturer in question, within a timeframe it deems reasonable and appropriate, submit a complete re-evaluation file (Form A) and financially support the re-evaluation by paying the applicable fees.

3 ADMINISTRATIVE REQUIREMENTS

3.1 Authorization to Share Information

Document authorizing INESSS to disclose the information included in the application (one-way sharing) to Health Canada, the Canadian Drug Agency (CDA-AMC), the Pan-Canadian Pharmaceutical Alliance (PCPA), and the Quebec Ministry of Health and Social Services (MSSS). Please note that this document does not permit the sharing of information from Health Canada or the CDA-AMC to INESSS. Instead, manufacturers are invited to complete the consent form for the harmonized review process in this context and submit it to Health Canada and INESSS.

- Use the "Authorization to Share Information" letter template available on the INESSS website for drugs, blood system products, and medical devices related to drug administration.
- Submit the consent form for the harmonized review process as part of the evaluation application.

3.2 Notice of Compliance issued by Health Canada

Notification issued pursuant to subsection C.08.004(1)(a) and indicating that the manufacturer or sponsor complies with sections C.08.002 or C.08.003 and C.08.005.1 of *the Food and Drug Regulations*. A Notice of Compliance is issued by Health Canada if the submission is deemed compliant following a comprehensive review.

- In the case of a generic drug for which the reference product does not appear on the Notice of Compliance, an explanation is required.

Note that this requirement must be met so that INESSS can submit its recommendation to the Minister.

3.3 Certificate of Registration for a Medical Device issued by Health Canada

Document issued by the Medical Devices Bureau of Health Canada's Therapeutic Products Directorate pursuant to section 36 of *the Medical Devices Regulations*. This certificate is also known as *a "Medical Device License*."

3.4 Certificate of Availability / Confirmation of Submission to the Pan-Canadian Pharmaceutical Alliance (PCPA)

Document confirming that the product is commercially available on the Quebec market in sufficient quantities, that the manufacturer can meet the demand that can reasonably be anticipated in Quebec, and, for the second letter template, that the manufacturer has

previously submitted a price determination request to the Pan-Canadian Pharmaceutical Alliance (PCPA) for this product.

- Use the Certificate of Availability letter template available on the INESSS website for requests that require this document.
- Use the Confirmation of Submission to the Pan-Canadian Pharmaceutical Alliance (PCPA) letter template for all applications to list multi-source products on the RGAM *Drug List*.

3.5 Samples

- Samples, illustrations (e.g., to support the calculation of the active surface area), or explanatory videos—for example, for certain dressings or devices—may be requested by INESSS upon receipt of the application or during the evaluation process.
- If so, these samples must be sent to INESSS headquarters at 2535 Laurier Blvd.,5th floor, Québec, Québec G1V 4M3.

3.6 Labels

- Provide the labels related to the product to be evaluated, including, for example, the labels on the bottle or cardboard packaging.
- Also provide the package inserts to be included in the packaging, if applicable.

For an application submitted prior to the issuance of a Notice of Compliance, submit draft labels, if available. For a drug, the *Drug Identification Number* (DIN*)* must appear on the final labels.

During the evaluation process, it is the manufacturer's responsibility to provide the final labels or confirmation that the product's draft labels have been approved by Health Canada. This requirement must be met so that INESSS can submit its recommendation to the Minister of Health.

3.7 "Application for Drug Registration" Form

This form is used for both registration on the RGAM *Drug List* and the *Drug List – Institutions*. The form also serves as the legal declaration by which the manufacturer guarantees the selling prices of the drugs it wishes to have listed on the *Drug List*. This is the guaranteed selling price (GSP).

- Use the "Application for Drug Listing" form available in French on the INESSS website (under "Application for Listing").
- A separate form must be submitted for each dosage form and strength of the same drug.

Here is the information you need to fill out the form:

A) Description of the drug

- Enter the **Drug Identification Number (DIN)** assigned by Health Canada. Enter "to be determined" if it is awaiting a notice of compliance.
- Enter the **applicant's name** as listed in Appendix A of *the Administrative Guide – RAMQ Drug List*.
- Enter the **trademark (brand name)** of the drug. If the application is submitted pending Health Canada's Notice of Compliance, the expected trademark must be indicated. If this is confidential, please indicate *"confidential"* in parentheses following the trademark. For a compress dressing, enter the trademark followed by its dimensions and active surface area in parentheses—e.g., 15 cm x 15 cm – 100 $cm^2$for a bordered dressing. For a wick-type dressing, enter the trademark followed by its length in linear centimeters in parentheses.
- List the **generic name** of the drug in French and, if applicable, as listed in the RGAM *Drug List* or the *Drug List – Institutions*. Additionally, if it is a salt, indicate this in parentheses – e.g., timolol (maleate).
- Enter the **dosage form** of the medication (e.g., tablet, capsule, syrup, ointment, cream), as listed in Appendix G of the RAMQ *Administrative Guide – Drug List*.
- Enter the drug's **strength** – e.g., 1 mg, 20 mg/0.5 mL, 25 mg/mL (3 mL), 7,500 IU, 250 mL, 5%:
  - for a compress dressing: the different active surface area ranges to be entered are:
    - less than 100 cm^2;
    - 100 cm^2 to 200 cm^2 ;
    - 201 cm^2 to 500 cm^2 ;
    - more than 500 cm^2 .
  - For a wick-type dressing: enter the value corresponding to its length—possible values: 1 m, 30 cm to 90 cm, or another value if different;
  - For dressings intended for the sacral region: enter "Sacrum."
- Enter the **AHFS Class:** category of the classification system developed by the American Hospital Formulary Service. This is the pharmacotherapeutic classification currently used for the publication of the RGAM *Drug List* and the *Drug List – Institutions*.
- Enter the **ATC Code:** category of the World Health Organization's (WHO) Anatomical Therapeutic Chemical classification system. This classification groups drugs based on the system or organ on which they act, as well as their chemical

and therapeutic properties. It is available on the WHO website and on the Health Canada website.

- Check the category to which the drug belongs: prescription [Pr] or non-prescription [nonPr], controlled drug, narcotic, or targeted substance.

B) List for which the request is being made

- Indicate, by checking the appropriate box(es), whether you are requesting that your product be listed on the RGAM *Drug List* or the *Drug List—Institutions*.

C) Indication recognized by Health Canada

- Enter the therapeutic indication recognized or requested from Health Canada, in the case of a drug awaiting a notice of compliance. For the evaluation of a therapeutic product whose evaluated indication is not included in the Canadian product monograph, enter the intended use.

D) Indication Requested from INESSS

- Indicate, by checking the appropriate box(es), whether the indication requested from INESSS is more restricted than that of Health Canada. If so, a justification for the choice of the target population is required and must be accompanied by supporting clinical data.

E) Guaranteed selling price (GSP) or submitted selling price for each format

- Upon submission of the recommendation to the Minister, the selling price will be deemed to be in the public domain. A justification supporting the maintenance of its confidentiality following the recommendation may be submitted to INESSS for review. The justification must be included in the “Summary Description of the File” form. Please note that the price will automatically become public domain upon the product’s inclusion on the RGAM *Drug List*.
- For each format, enter the recommended retail price (RRP) for pharmacists in Canadian dollars for all applications for inclusion on the RGAM *Drug List*. If the product is sold only through a wholesaler, still enter a pharmacist’s PVG, which must be identical to the wholesaler’s PVG. If the listing is intended only for the *Drug List – Institutions*, enter “N/A” in the pharmacist’s PVG field. Note that the number of formats is generally limited to two, with the exception of strips, topical products, solutions, and suspensions, for which the number of formats is limited to four. The unit price of the product for each of the different formats must be the same.
- For each format, enter the drug’s wholesale price (WPP) in Canadian dollars (RGM *Drug List*) or the submitted price (*Drug List – Institutions*).
- For each format, indicate the discount percentage granted to wholesalers, which corresponds to the difference between the price charged to pharmacists and the price charged to wholesalers. Enter 0% if applicable. The difference between the

price charged to pharmacists and the price charged to wholesalers may vary from one product to another. This difference may not exceed the maximum authorized margin (6.50%). If the product is not sold through a wholesaler or if its listing is intended only for the *Drug List – Institutions*, enter "N/A" in the box.

- For any application for listing on the RGAM *Drug List*, indicate whether or not to authorize adjustment to the lowest price (PPB). Note that if the YES box is checked, the price will be automatically adjusted to the lowest price submitted by other manufacturers of a drug in the same category. This new adjusted price will become your MRP. This method does not apply to the *Drug List – Institutions*. Unless otherwise notified by INESSS following the evaluation of a manufacturer's request for exemption from the application of the LBP method, this authorization will remain valid for subsequent updates to the RGAM *Drug List*.
- Indicate the selling price to healthcare facilities (hospitals) in Quebec. It may not exceed the PVG for pharmacists if the product's listing also applies to the RGAM *Drug List*.

F) Applicant's contact information and certification

- Enter the applicant's full contact information (name, address, email, phone number).
- Sign and date the certification stating that all information provided complies with the conditions to which the applicant has committed. Enter the contact information of the person signing the certification. If this form needs to be modified later by the manufacturer, it must be signed and dated again. This certification may be signed by any authorized person, at the discretion of the manufacturer's . The certification will be considered valid even if it is not signed by the person responsible for the file or the one submitting the application.

3.8 Form "Application to Add a Blood System Product"

This form is used to add a product to the *PSS List*.

- Use the "Request to Add a PSS" form, available in French on the INESSS website (under "Registration Request").
- A separate form must be submitted for each dosage form and strength of the same product.

Here is the information needed to complete the form:

A) Product description

- Enter the **PSS identification number (DIN)** assigned by Health Canada. Enter "to be determined" if it is awaiting a notice of compliance.

- Enter the **applicant's name** as listed in Appendix A of *the Administrative Guide* – RAMQ *Drug List*.
- Enter the product's **trademark (trade name)**. If the application is submitted pending Health Canada's Notice of Compliance, the expected trademark must be indicated. If this is confidential, please indicate *"confidential"* in parentheses following the trademark.
- List the active ingredients of the blood system product in French.
- Enter the **form, format, and strength** of the product as specified in Appendix G of *the Administrative Guide* – RAMQ *Drug List*
- List the donor origin and the human products used in the product's manufacturing process, if applicable.

B) Indication recognized by Health Canada

- List the therapeutic indication recognized or requested from Health Canada in the case of a product awaiting a notice of compliance.

C) Indication requested from INESSS

- Confirm, by checking the appropriate box(es), whether the indication requested from INESSS is more restricted than that of Health Canada. If so, a justification for the choice of the target population is required and must be accompanied by supporting clinical data.

D) Submitted retail price for each format

- For each format, enter the selling price in Canadian dollars for any application to add *the product* to the *Blood System Product List*.

E) Applicant's contact information and certification

- Enter the applicant's full contact information (name, address, email, phone number).
- Sign and date the certification stating that all information provided complies with the conditions to which the applicant has committed. Enter the contact information of the person signing the certification. If this form needs to be amended later by the manufacturer, it must be signed and dated again. This certification may be signed by any authorized person, at the manufacturers' discretion. The certification will be considered valid even if it is not signed by the person responsible for the file or the one submitting the application.

3.9 Form "Application for Registration of a Medical Device Related to the Administration of Medications"

This form is used for registration on the RGAM *Drug List* and the *Drug List – Institutions*. The form also serves as the legal certification through which the manufacturer guarantees the selling prices of the drugs it wishes to have listed on the RGAM list. This is the guaranteed selling price (GSP).

- Use the "Application for Registration of a Medical Device Related to Drug Administration" form available in French on the INESSS website (under "Application for Registration").

Here is the information needed to complete the form:

A) Product description

- Enter the device's approval number
- Enter the **applicant's name** as listed in Appendix A of *the Administrative Guide* – RAMQ *Drug List*.
- Enter the **trademark (trade name)** of the product.

B) List for which the application is being submitted

- Please indicate, by checking the appropriate box(es), whether you are requesting that your product be included on the RGAM *Drug List* and/or the *Drug List for Institutions*

C) Indication Requested from INESSS

- Indicate, by checking the appropriate box(es), whether the indication requested from INESSS is more restricted than that of Health Canada. If so, a justification for the choice of the target population is required and must be accompanied by supporting clinical data.

D) Submitted retail price for each dosage form

- For each format, enter the selling price in Canadian dollars for any application to be added to the list.

E) Applicant's contact information and certification

- Provide the applicant's full contact information (name, address, email, phone number).
- Sign and date the certification stating that all information provided complies with the conditions to which the applicant has committed. Enter the contact information of the person signing the certification. If this form needs to be modified later by the manufacturer, it must be signed and dated again. This certification may be signed by any authorized person, at the manufacturers' discretion. The certification will be

considered valid even if it is not signed by the person responsible for the file or the one submitting the request.

3.10 Form "Summary Description of the Dossier "

Form developed by INESSS, which must be submitted if the form requires this document.

- Drug: Use the most recent version of the "Summary Description of the File" form, available on the INESSS website.
- PSS: Use the most recent version of the "Summary Description of the File – PSS" form, available on the INESSS website
- DM: Use the most recent version of the "Summary Description of the File – DM" form, available on the INESSS website
- Biosimilar: Use the most recent version of the "Summary Description of a Biosimilar Drug" form, available on the INESSS website.

3.11 Cover Letter

This is a cover letter for the application, which must be written in French. The following information must be included:

- Consultant authorized to communicate with INESSS regarding the file.
- Contact information for the person responsible for the file. The contact information for a second contact person may be included, if desired.
- Name of the reference product, along with its approval status with Health Canada—for an application concerning a biosimilar or generic drug.
- If applicable, indicate that the drug or blood system product must be administered in combination with another product that is not listed.

3.12 Proof of Marketing

- If the product does not have a DIN (e.g., bandages, nutritional formulas, natural health products), provide an invoice proving the sale of the product in Canada to community pharmacists, wholesalers, or healthcare facilities.

3.13 Listing status in other provinces

- Provide a list of the product's coverage status in other provinces, including any special provincial or federal programs.

  If the product is listed with restrictions, provide a list of the criteria that must be met for reimbursement of these medications.

- If any changes in status occur during the evaluation period, please forward the information as soon as possible to INESSS via email atinscription@inesss.qc.ca .

4 CLINICAL COMPONENT REQUIREMENTS

4.1 Posters, abstracts, or oral presentations related to the main studies submitted

Such supporting documents may be submitted exclusively if they are associated with the published primary clinical studies (or available as a manuscript for publication). For example, these may include quality-of-life or survival data.

- Please clearly identify the study to which the documents relate and place them in a subfolder labeled “Posters or Abstracts.”

Conference posters and abstracts related to studies that have never been published will not be accepted.

4.2 Appendices, supplements, errata, or editorials

Submit documents related exclusively to published primary clinical studies. Supplements for all primary clinical studies must be submitted.

- Please clearly identify the documents and place them in a subfolder titled “Other Publications.”

4.3 Evidence-based rationale, including comparative bioavailability data or clinical data regarding the multi-source product under study

When submitting the application, provide a rationale including comparative clinical data for the product subject to the application for exemption from the lowest price method (LPM) compared to one or more of the generic products under review. This may include bioavailability data or other clinical data.

4.4 Indirect comparison

In the absence of a direct comparative study between the subject under investigation and the most relevant comparator(s) (see Section 4.5 “Comparators”), one or more indirect comparisons, whether published or unpublished, must be submitted. **These indirect comparisons, whether published or unpublished, must be included in the five studies, publications, or documents submitted.**

- In the case of an unpublished comparison, provide the complete reports of the systematic literature review and the feasibility assessment. The systematic literature review should ideally have been conducted during the year preceding submission. In addition, the report on the indirect comparison may be written using the template

provided in Appendix VII. This report should include, in particular, the following elements:

- the statement and rationale for the objectives of the indirect comparison;
- the link to the registration of the indirect comparison protocol;
- a detailed description and justification of the selection criteria for relevant studies using the PICOS approach *(P = Population, I = Intervention, C = Comparator(s), O = Outcomes, S = Study design);*
- a description of the data sources used, including bibliographic databases and grey literature;
- structured and detailed search strategies according to the data sources used;
- a description of the process for selecting relevant studies;
- a description of the data extraction process and a list of the data used;
- a description of the assessment of the methodological quality of the selected studies (assessment process and tools used, as well as a table of assessment results);
- a list of *the outcomes* of interest evaluated*,* indicating efficacy, safety, and impact on quality of life, along with a description of the reasons for exclusion, if applicable;

a description of the comparability of the studies included in the indirect comparison ( );

- a description of the sources of heterogeneity;
- a detailed description and justification of the statistical methods used for the primary and sensitivity analyses;
- the design of the intervention network for the indirect comparison and the justification for the comparators used;
- a description of the method used to identify prognostic factors and potential effect modifiers ;
- detailed results of all analyses performed (description, tables, and figures);
- an exploration of sources of heterogeneity and a description of the methods used (e.g., subgroup analysis);
- a description of the robustness of the results, particularly taking into account the risks of bias and the methodological choices that were made;
- a description of the methodological limitations of the analyses conducted and their impact on the indirect comparison;

- a conclusion regarding the main results of the indirect comparison.

For informational purposes, upon publication of the opinion, the INESSS's qualitative analysis and assessment of the indirect comparison will be published. However, the quantitative data will be redacted.

- In the case of a published indirect comparison, provide the publication and its supplements.
- If an indirect comparison would be relevant but is impossible to conduct, provide a rationale documenting the factors justifying the impossibility of conducting such a comparison. If, during the evaluation, INESSS determines that the submitted rationale is insufficient, a request may be made to the manufacturer to obtain such a comparison.

4.5 Comparators

Relevant comparators are expected to be those that will eventually be replaced or displaced by the product under evaluation. They must:

- be listed in the regular section of the *Drug List* or the *Drug List – Institutions* and represent the standard of care for the condition being evaluated;

  or

- be listed in the exception drugs section of these lists, with a recognized indication related to the one requested;

  or

- be listed on the *Quebec Blood System Products List*. They may or may not currently be distributed by Héma-Québec.

If the most relevant comparator(s) are best supportive care or if no treatment is available, a placebo will be accepted as a comparator. A brief justification must accompany the choice of this or these comparators. If the drug being evaluated is a commercial formulation intended to replace a compounded preparation—that is, an extemporaneous mixture of a drug or a product for compounding (Section 3.2 of the *Drug List*)—this formulation must be considered a comparator.

Special cases: relevant but non-listed comparators

Drugs, medical devices, or blood system products not listed on the lists that will be re d or would be replaced or displaced by the product under evaluation will also be considered relevant comparators. This comparison will allow INESSS to conduct additional analyses and inform the Minister in the event of their listing; it cannot be the only comparison submitted. Examples include:

- a medication, a compounded preparation, a medical device, or a health service product (HSP) that is reimbursed on an exceptional basis by the Régie de l'assurance maladie du Québec (RAMQ) through the "exceptional patient" measure or by healthcare facilities under exceptional access measures, such as exceptional treatment (e.g., Health Canada's Special Access Programs) and specific medical necessity;
- a non-pharmaceutical intervention; or
- a drug, medical device, or health service that has been the subject of a listing recommendation in which its therapeutic value has been recognized (including a promise of value/promising nature), in a **notice published 120 calendar days or more** prior to the submission of the listing application, unless it was the subject of a decision by the Minister to refuse listing.

If these comparators have never been evaluated by INESSS or if their therapeutic value has not been recognized by INESSS, the manufacturer must submit a review of the scientific literature pertaining to the data so that the efficacy and safety of these comparators can be assessed and taken into account in its analyses.

4.6 Product Description

For products that do not have an official monograph, the following information must be provided:

- A document presenting the product profile and its instructions for use *(Prescribing Information)*.
- For dressings, a detailed description of the dressing's composition, properties, and treatment indication, documenting its differences from comparable dressings, if applicable.

4.7 Data demonstrating the precision and accuracy of the results

- Submit data reporting test results in accordance with the applicable ISO standards for these devices—e.g., ISO 15197:2013 for blood glucose test strips.

4.8 Real-world data

To support the evaluation of the subject under study, whether during an initial evaluation or a re-evaluation of a product or indication, results from real-world studies may be submitted. It should be noted that the submission of this type of data does not replace the requirement to submit at least one published clinical study or a study available as a manuscript for publication (see Section 4.9) for an initial evaluation. During a re , it is possible to submit only real-world studies, but these data must address the uncertainties raised during the previous evaluation.

Additional information on the details required when submitting real-world evidence is provided in Appendix V.

4.9 Published clinical studies or manuscripts for publication

At least one randomized, controlled clinical study that has been published or is available as a manuscript for publication must be submitted.

- An explanation is required to clarify why another quote was selected.
- A confidentiality agreement may be established on an exceptional basis if the publication is subject to an embargo.
- If the submission is prioritized by Health Canada, the manuscript for publication may be forwarded as soon as possible and no later than 30 calendar days following the decision on admissibility.

Reminder: Please name electronic files as follows: Title (usually the study name), first author's name, year.

Studies must include relevant clinical outcome measures associated with the medical condition targeted by the drug, and double-blind studies are preferred.

- From among the submitted studies, select the most relevant ones—up to a maximum of 5—and organize and describe them by filling out the boxes in the clinical section of the form: "Summary Description of the Dossier," tailored to the subject of the evaluation (drug, biosimilar, PSS, DM). **Reminder: Indirect comparisons, whether published or unpublished, must be included among the 5 studies submitted.**
- When a clinical study available as a manuscript for publication is submitted with the application, it is the manufacturer's responsibility to forward the official publication as soon as possible.
- Provide an electronic version of the complete *Clinical Study Report* (CSR*)*, including appendices, figures, and tables, for the main clinical studies that have been published or are available as a manuscript for publication. The entire report must be submitted. It must contain, at a minimum, the complete protocol (including protocol amendments, if any) and the detailed statistical plan.

Other publications may be appended, such as documents describing the scales and questionnaires used in clinical trials and expert guidelines. Access to a French version of the main measurement scales or questionnaires used is recommended, with references provided.

Special Cases

- *Request for Re-evaluation (Refusal of Registration on Therapeutic Grounds)* – If the application concerns a drug, a blood product, or a medical device related to the administration of a drug that was refused registration on therapeutic grounds, provide new relevant clinical data as well as a rationale addressing the grounds that led to the decision to refuse recognition of therapeutic value. Please note that clinical data already provided and previously evaluated do not need to be

resubmitted. Economic studies must be updated to include the new clinical data, as well as any other documents supporting the evaluation of the five aspects required by the INESSS Act.

- *Request for Re-evaluation (Refusal of Registration for All Aspects)* – If the request concerns a drug, a blood product, or a medical device related to the administration of a drug that was refused registration for all aspects, the clinical requirements apply only if new clinical data are used in the economic studies. The new data submitted must address the uncertainties or concerns raised during the refusal of registration of the previous evaluation.
- *Request for Reassessment (clinical follow-up)* – If the request is made following a process of monitoring real-world care data (clinical follow-up condition; promising nature/promise of therapeutic value), provide relevant new clinical data and an update to the previously submitted economic studies, accompanied by any other documents supporting the evaluation of the five aspects provided for by INESSS legislation.
- *Request for Re-evaluation (for a generic or biosimilar drug for which the innovator product has been denied marketing authorization)* - Submit all available and relevant clinical data, whether publicly accessible or not, for both your product and the innovator product.
- *Application for evaluation (for a generic drug or biosimilar drug for which the innovator product has never been evaluated)* - Submit all available and relevant clinical data, whether publicly accessible or not, for both your product and the innovator product.
- *Comparator* – When the therapeutic value of a relevant comparator has been recognized by INESSS 120 calendar days or more prior to the submission of the application for listing and the Minister has deferred a decision at the time of submission, this comparator must also be included in the comparison.
- *Indications requested by the manufacturer that are narrower than those granted by Health Canada* – In this case, the clinical data supporting this request must be provided. This may include, for example, data from subgroups within the target population.
- *Manufacturer's application for the registration of a product intended for a subgroup of patients among those included in one or more clinical studies* – In this case, provide a comprehensive analysis report including, in particular, the following:
    - the rationale for the analysis;
    - a detailed table presenting the baseline characteristics of the subjects, broken down by assigned treatment option;
    - the clinical results associated with the subgroup, accompanied by statistical analyses such as the statistical analysis plan and details of the statistical method used—interaction test, adjustment for multiple testing, etc.

- *Applications for the registration of a new strength, a new presentation, or a new dosage form* – In certain cases, a pharmacokinetic study, whether published or not, may be sufficient.
- *Applications for an iterative version of a medical device* – In the case of an update to an already registered device (e.g., an evolution of the same technology), where the device's efficacy, safety, and price remain similar, a comparison with the previous version and performance data are sufficient.
- *Third-party data* – When the drug's notice of compliance is based on third-party data, provide the systematic review submitted to Health Canada, the relevant scientific data, and the unredacted review reports from foreign authorities, where applicable.
- *Evaluation Pending a Health Canada Notice of Compliance* – When the indication granted by Health Canada differs from that evaluated by INESSS, new clinical data or economic analyses may be required and requested by INESSS.

4.10 Justification of Relevance

- For dressings, nutritional formulas, diagnostic agents, and drug combinations already listed, provide a rationale justifying the clinical relevance of each product.

4.11 List of clinical studies, published or unpublished, including those currently underway

- Provide a list of clinical studies, published or unpublished, including those currently underway, along with official or expected publication dates, pertaining to the drug for the requested therapeutic indication. The following information is preferred:
  - start and end dates of the studies;
  - complete references;
  - articles associated with each study;
  - any other relevant information.

4.12 User Manual

For a medical device (MD) related to the administration of a drug:

- Submit the French version of the user manual or, if the French version is not yet available, the English version. The French version must be provided as soon as possible.
- It is the manufacturer's responsibility to inform INESSS as soon as possible of any relevant changes to the user manual, whether during the evaluation process, after a recommendation, or following registration.

4.13 Official Product Monograph

- Submit the French version of the official product monograph or, if the French version is not yet available, the English version. The French version is expected as soon as possible.
- The draft monograph submitted to Health Canada is required for applications filed prior to the issuance of the Notice of Compliance.
- It is the manufacturer's responsibility to inform INESSS as soon as possible of any relevant changes to the monograph, whether during the evaluation process, after a recommendation, or following registration.

4.14 Proof of bioequivalence or biosimilarity

Document certifying that the generic product is bioequivalent to the innovator product according to Health Canada standards.

- Provide the Health Canada Notice of Compliance that lists the reference product.
- If the Notice of Compliance does not name a reference product or if the reference product has never been listed on the drug lists and the generic product is subject to a cross-license, provide a letter from both manufacturers confirming that the product is subject to a cross-license with a product that is currently listed or has previously been listed.
- If the Notice of Compliance was issued without mentioning a reference product and if the generic product is not cross-licensed, submit additional data to assess the bioequivalence of the product—e.g., report, summary of bioequivalence study results submitted to Health Canada to obtain the Notice of Compliance, clinical study establishing clinical equivalence, description of the delivery device.

4.15 Health Canada Reviewers' Report

Regulatory document evaluating a new drug by Health Canada.

- Submit the clinical section of the Health Canada Reviewers' Report that comments on and analyzes the clinical studies submitted by the manufacturer when applying for product approval or a product monograph amendment *(Clinical Reviewer's Report, Statistical Reviewer's Report)*. If this report is not available at the time of submission, submit it as soon as possible during the review process once it becomes available.
- Provide the content of Health Canada's requests for clarification *(Clarimails* and *Clarifaxes)* regarding clinical data and the product monograph. A summary of the questions and answers may also be submitted as a supplement.
- For any application submitted prior to the issuance of Health Canada's Notice of Compliance, provide all clarifications and responses submitted (for the clinical

section) after the filing of the application, regardless of whether the review is harmonized or not.

4.16 Clinical Executive Summary

A document prepared by the manufacturer summarizing the most important clinical information regarding the application. **This executive-format document should be no more than 25 pages, but ideally fewer than 10 pages**. It should include the following information:

- Disease context (with references):
  - Quebec or Canadian epidemiological data,
  - a brief description of the disease,
  - currently administered treatments. We would like to include a figure (algorithm) showing the treatments available on the lists along with their intended use.
- Brief description of the treatment under evaluation;
- Summary of clinical data—efficacy, safety, quality of life, therapeutic characteristics. In addition, the following information is requested:
  - in the case of a rare disease or an orphan disease, a description of the main clinical parameters is required;
  - When a new clinical evaluation parameter is being used for a known condition, this should also be described. In these situations, an explanation of the main measurement scales or questionnaires used is expected. Access to a French version of the main measurement scales or questionnaires used is recommended.
- The place of the therapy under evaluation within the therapeutic arsenal according to the indication requested from INESSS:
  - reasons for this position.

4.17 Detailed Summary – Clinical Studies Section (2.7.3)

Clinical section of the document submitted by the manufacturer to Health Canada when applying for product approval or a product monograph amendment *(Comprehensive Summary)*.

5 ECONOMIC SECTION REQUIREMENTS

5.1 Pharmacoeconomic study

An analysis aimed at evaluating the efficiency of an intervention under study, i.e., the ratio of its incremental cost to its incremental clinical outcomes compared to other options with the same therapeutic intent. The analysis should be based on the best available methodological practices at the time of submission and comply with the INESSS guidelines on economic evaluations (INESSS, 2025). In addition, it should be accompanied by a review of the scientific literature listing studies that have evaluated the cost-effectiveness of the subject under study or other drugs, blood products, or medical devices related to the administration of a drug for the recognized indication, the requested indication, or a related indication.

- Submit a pharmacoeconomic study that includes at least one analysis for the indication recognized by Health Canada and one for the indication requested for reimbursement in Quebec, if the two differ. If it is not possible to conduct an analysis for the indication recognized by Health Canada, a justification detailing the obstacles, constraints, or limitations encountered must be provided. The quality, rigor, and adequacy of this justification will be analyzed by INESSS once the application is deemed admissible and activated. If, during the evaluation, the justification is deemed insufficient, INESSS may contact the manufacturer to obtain an additional analysis, which could result in delays in the evaluation process.
- The pharmacoeconomic study must be accompanied by a review of the scientific and economic literature, **and the references cited therein must be presented**.
- The main analysis of the study must focus on **comparators listed on one of the lists**. Scenario analyses with other relevant comparators may accompany this analysis (see section 4.5).
- If a companion test is required, it must be considered within the pharmacoeconomic study.
- Provide a functional Excel spreadsheet containing the model, calculations, and results supporting the pharmacoeconomic analysis. Where applicable, embedded macros should be accessible without restriction. **The file must be self-contained with no external links (e.g., source of a variable, reference in a macro).** When a probabilistic analysis is submitted, it must be functional, error-free, and capable of being executed **within a reasonable timeframe**, considering that a workday is 7 hours. If this timeframe cannot be met, INESSS reserves the right to request a new analysis, which could result in additional delays.
- Complete the section on the description of the pharmacoeconomic study in the “Summary Description of the Dossier” form tailored to the subject of the evaluation (drug, biosimilar, PSS, DM), if applicable.

- **Comply with the requirements of Annex I and use the normative values documented in Annex IV. Otherwise, provide a justification for non-compliance.**

Special Cases

- *Pharmacoeconomic analysis* – The submitted model may be based on a platform other than Excel, provided that a justification supports this choice. However, INESSS reserves the right to reject an analysis using software other than a spreadsheet. Regardless of the platform chosen, transparency remains essential to facilitate evaluation and ensure the traceability of methods and results.
- *Cost-consequence analysis* – If a cost-consequence analysis is submitted and the justification provided for the absence of a cost-utility or cost-minimization analysis is deemed insufficient during the evaluation, INESSS may request an acceptable cost estimate (Appendix II).
- *Biosimilar drug whose generic name has not been evaluated for the intended indication, nutritional formula, dressing, new strength, presentation, or form of a drug, and diagnostic agent* – When the only comparators these products seek to replace are those with the same generic name, a pharmacoeconomic study is not always required; the "Price Justification" or "Summary Description of the File" document, tailored to the subject of the evaluation (drug, biosimilar, PSS, MD), may be sufficient. In the section on the pharmacoeconomic study, indicate the reasons for its absence and include a reference to the price justification document.
- *Relevant comparators* – When the therapeutic value of a relevant comparator has been recognized by INESSS 120 calendar days or more prior to the submission of the listing application and the Minister has deferred his decision at the time of the application's submission, this comparator must also be included in the pharmacoeconomic analysis.
- *Request for Reassessment (Refusal of Listing for All Aspects)* – If the application concerns an assessed product that was the subject of a recommendation to refuse listing for all aspects, provide a pharmacoeconomic analysis, which may be an update of the previous analysis. In certain circumstances agreed upon in advance with INESSS, it may be possible to provide authorization to use the previous pharmacoeconomic model.
- *Evaluation pending a Health Canada notice of compliance* – When the indication granted by Health Canada differs from that evaluated by INESSS, an update to the pharmacoeconomic study may be requested by INESSS.
- *Request for Re-evaluation (Clinical Follow-up)* – If the request is made following a real-world data monitoring process (clinical follow-up condition; promising nature/promise of therapeutic value), provide an update to the previously submitted pharmacoeconomic study. Please note that INESSS may require the consideration of other relevant comparators.

The elements listed below must be clearly explained and supported in the submitted study:

- type of analysis;
- objective, context, and target population;
- comparator;
- perspective;
- sources of input data (clinical, utility, economic);
- time horizon and discount rate;
- outcome measures and implications of uncertainty.

Additional information regarding methodological requirements is presented in Appendix II.

5.2 Budgetary Impact

The purpose of this analysis is to estimate the effect of changes anticipated by the listing of a drug, a blood product, or a medical device related to drug administration on the budget of the RAMQ, healthcare facilities, or the Ministry of Health and Social Services. These changes between the *status quo* scenario and the listing scenario may result in additional costs or cost reductions (savings). This analysis should be based on the best available methodological practices at the time of submission. The elements listed below must be clearly explained and supported in the submitted study.

- Provide a budget impact analysis report along with a functional Excel spreadsheet containing the calculations and results. **Additionally, the file must be self-contained and free of any external links (e.g., source of a variable, reference within a macro).** All references cited and used to support the analysis's assumptions must be listed.
- Complete the table of key assumptions and the table(s) (if a companion test is included) of the budget impact analysis results in the form "Summary Description of the File" tailored to the subject of the evaluation (drug, biosimilar, PSS, DM).
- **Comply with the requirements of Annex I and use the normative values documented in Annex IV. Otherwise, provide a rationale justifying non-compliance.**

The elements listed below must be clearly explained and supported in the submitted analysis:

- target population in the evaluation request;
- time horizon and perspective;
- market size, methodological approaches, and projections;
- market shares;

- costs of drugs, blood system products, or medical devices related to drug administration, or other costs; outcome measures and implications of uncertainty.

The results of the budget impact analysis must be presented by 12-month periods and for the total number of years, and broken down by the relevant budget: RAMQ, healthcare facilities, or the Ministry of Health and Social Services in the case of a blood system product. At a minimum, three types of results must be highlighted in a table.

- Gross budgetary impact: corresponds to the specific expenses related to the acquisition of the drug, blood system product, or medical device associated with the administration of the drug under study, regardless of the impact on other expenses. This impact specifically excludes the wholesaler's profit margin as well as the cost of the pharmacist's professional services. In the case of combination therapy, this impact must be broken down by drug.
- Market share: corresponds to the anticipated number of distinct patients treated with the product under evaluation, the anticipated number of prescriptions, or the number of reimbursed units.
- Net budgetary impact: corresponds to the additional or reduced cost associated with reimbursement, i.e., the difference between the current situation and the situation that takes into account the listing of the drug, blood product, or medical device related to the administration of the drug under study. As applicable, it accounts for costs related to the pharmacist's professional services and the wholesaler's profit margin.

Special Case

- *Request for Re-evaluation*
  - If the request concerns an assessed item that was the subject of a recommendation to deny listing for all aspects provided for by law, provide a budget impact analysis, which may be an update of the previous analysis.
  - If the request is made following a real-world data monitoring process (clinical monitoring condition; promising nature/promise of therapeutic value), provide an update to the previously submitted budget impact analysis.
- *Evaluation pending a Health Canada notice of compliance* – When the indication granted by Health Canada differs from that evaluated by INESSS, new economic analyses may be required and requested by INESSS.

Additional information regarding methodological requirements is provided in Appendix III.

5.3 Price Appropriateness

This document summarizes, in a table, the unit price, the intended dosage, and the cost of treatment associated with the use of the product under evaluation and its comparators.

These costs are compared on a common basis or over a common period, such as per time period, per cycle, per injection, per treatment, per kilocalorie, per cm^2, etc.

- Complete the table on price appropriateness in one of the “Summary Description of the File” forms appropriate for the subject of the evaluation (drug, biosimilar, PSS, MD).
- Comply with the requirements of Appendix I and use the INESSS normative values documented in Appendix IV. Otherwise, provide a rationale justifying the deviation.

Additional information regarding the requirements, particularly from a methodological perspective for drugs only, is provided in Appendix I.

6 REQUIREMENTS FOR THE "OTHER INFORMATION" SECTION

6.1 Health Need

Justification outlining the unmet need not addressed by treatments currently administered in Quebec. Relevant information must include the following elements:

- Impact of the medical condition:
  - symptoms;
  - effects of the disease on quality of life, functional independence, and life expectancy.
- Standard treatments in Quebec:
  - advantages and limitations of existing treatments;
- Submit a rationale outlining the unmet health need;
- Complete the "Health Need" box in Section 4 "Other Information" of the "Summary Description of the File" form, tailored to the subject of the evaluation (drug, biosimilar, PSS, DM), with a summary of the main points.

6.2 Effects on public health

A statement of up to 5 pages outlining how the drug, blood product, or medical device used to administer a drug is expected to benefit the Quebec population. Relevant information may include the following:

- Quebec or Canadian data used to establish the incidence or prevalence of the medical condition targeted by the indication of the item under evaluation;
- The burden of the disease in a Canadian or Quebec context from a societal or public health perspective—e.g., the cost of the disease to the health and social services system and the societal cost;
- Anticipated benefits associated with the subject of the evaluation, from a social or public health perspective, for example:
  - reduction in the burden on family caregivers;
  - reduction in harm (e.g., crime, poisoning);
  - reduction in the spread of the disease within the population;
  - presenteeism at school or work;
- reduction in the environmental footprint (e.g., sustainability, energy consumption, carbon footprint, waste management, resource use). If relevant, risk of suboptimal use of standard treatments or the subject under study.

- Submit a rationale outlining the effects of the subject under study on public health.
- Complete the “Other Information” section of the “Summary Description of the File” form tailored to the subject of the evaluation (drug, biosimilar, PSS, MD) with a summary of the main elements.
- Consequences or adverse effects associated with the handling, reconstitution, or administration of the drug for the treating team.

Special Case

- *Request for Reassessment* – Resubmit this document. An update to the information submitted during the previous assessment may be provided, if applicable.

6.3 Effects on the health and social services system

A statement of up to 5 pages outlining the organizational impact on the health and social services system of reimbursing the drug, blood system product, or medical device related to the administration of the drug under study for the intended indication. Relevant information may include the following:

- Impact on human, material, and physical resources associated with the use of the evaluated item, as well as on the organization of care and services in Quebec, for example:
    - impact on the number of medical follow-ups;
    - impact on the use of interventions such as point-of-care testing or hospital laboratory services;
    - changes in how care is delivered, including the shift of patients from inpatient to outpatient settings.
- Impact on support for environmental sustainability (e.g., sustainability, energy consumption, carbon footprint, waste management, resource use, place of production).

Justification outlining the services offered by the manufacturer—e.g., patient support program, adherence program, private infusion clinics, etc.

- Submit arguments detailing the effects on the health and social services system.
- Indicate the relevant elements in the “Summary Description of the File” form tailored to the subject of the evaluation (drug, biosimilar, HCP, MD). When the use of the drug, blood product, or medical device related to drug administration does not result in a change in resource requirements or in the organization of care and services, the statement “No impact” must be entered in the box provided for this purpose.
    - Services Offered by the Manufacturer (Optional) – You will find a box in Section 4 of the form regarding effects on the health and social services system. In this box, if a patient support program is offered for your product (or

is planned), you will find four questions and two sub-questions to which INESSS would like to receive answers. You may indicate the confidentiality status of each of your responses. Please note that confidential information will be used for the scientific evaluation but will not be made public. If no such program exists for your product, please notify INESSS by checking the appropriate box.

Special Cases

- *Request for Re-evaluation* – Resubmit this document. An update to the information submitted during the previous evaluation may be provided, if applicable.

APPENDIX I

Methodological aspects regarding price appropriateness

Comparator – Relevant comparators listed on one of the lists (see Section 4.5) must be presented. Other relevant comparators may also be included, if justified.

Dosage regimen – The dosage regimen used to calculate the cost of treatment must be documented and referenced. It is typically based on the dosage recommended in the product monographs, and in certain situations, it may also be based on common clinical practice or real-world data.

Unit price and treatment cost – This price corresponds to the guaranteed selling price submitted by the manufacturer, the price listed on the *Drug List* or the lowest applicable price indicated, the price submitted by the manufacturer for reimbursement by healthcare facilities, or the price derived from healthcare facilities' supply contracts. When this price is unavailable, the price from a wholesaler or from previous INESSS notices may be used. In the event that a valid selling price for a comparator is unavailable, an approximate price derived from other Canadian sources may be used in the analysis. Note that, in its analysis, INESSS uses the confidential prices from the Government Procurement Center (CAG)'s purchase contracts, those provided by the Ministry of Health and Social Services, or those obtained from Héma-Québec.

Although INESSS may conduct additional economic analyses using other prices submitted by the manufacturer or any other proposed agreements that could affect treatment costs, under no circumstances may INESSS include prices that involve confidential discounts or rebates agreed upon through the Pan-Canadian Pharmaceutical Alliance or with the Ministry of Health and Social Services.

The treatment cost, meanwhile, combines the number of units required for a given treatment duration based on the dosage in question and the price per unit of the medication. It assumes perfect adherence and continuous use of the product. This cost must not take into account the financial contribution of insured individuals (deductible and coinsurance) who purchase this medication, nor the wholesaler's profit margin or the cost of the pharmacist's professional services. It must, however, account for potential medication losses based on, among other factors, the product's stability and the estimated dispensing volume.

For calculations based on weight or body surface area, refer to the normative values presented in Appendix IV.

APPENDIX II

Methodological aspects of pharmacoeconomic evaluation

This section outlines certain methodological aspects of pharmacoeconomic evaluation. The INESSS guidelines on economic evaluations (INESSS, 2025) can also serve as a guide.

Type of Analysis

Various proposals for pharmacoeconomic studies may be submitted. The choice of a proposal must be justified based on the clinical and economic context of the intervention under study.

When there is a differential therapeutic value, **cost-utility analysis** is preferred in order to account for multiple health outcomes in a single measure. It involves incorporating quality of life into the measurement of health outcomes, and its result is expressed as cost per quality-adjusted life year (QALY) gained. If such an analysis cannot be performed, a justification is required. Depending on the situation, a **cost-effectiveness analysis** may then constitute a sufficient approach. This involves linking the costs of a strategy to its quantitative outcomes. The result is expressed as cost per unit of incremental clinical outcome (e.g., life-year gained, clinical event or adverse event avoided).

In a situation where the product under evaluation is associated with demonstrated benefits similar to those of its comparators for an overall similar toxicity burden, **a cost minimization analysis** constitutes an acceptable approach. Clinical evidence supporting this comparability in terms of efficacy and safety must be submitted. This applies in particular in the context of a bioequivalence study (for generic drugs or biosimilars, for example) or similar results from a non-inferiority study or an indirect comparison. This analysis consists solely of comparing costs and allows for the evaluation of efficiency based on the least-cost option. The result is expressed in terms of incremental treatment cost. Note that the acquisition cost of the intervention is not the only relevant cost. In certain situations, other costs must be included if they differ between the options being evaluated, such as costs related to treatment administration, the use of medical resources, and productivity losses among patients or caregivers when a societal perspective is adopted.

When the compared interventions do not share a common denominator regarding effects on the patient and their health (outcomes) or if it is impossible to quantify the observed effects through a direct or indirect comparison, **a cost-outcome analysis** may represent an acceptable approach. Clinical and economic results are presented in a disaggregated manner, without any aggregation. However, due to the inherent limitations of this approach and a more subjective assessment of efficiency, this analysis is a last-resort option; it must be accompanied by a rationale— —justifying why a cost-utility or cost-minimization analysis is not a valid approach.

Purpose of the analysis, context, and target population

The objective of the pharmacoeconomic analysis must be clearly stated in the report, as must the target population. This population must correspond to the indication requested for inclusion on the *Drug List*, the *Institutional Drug List*, or an addition to the *Quebec Blood System Products List*. When it differs from the one requested or recognized by Health Canada, an alternative analysis, known as a scenario analysis, that corresponds to the population targeted by Health Canada, must also be submitted. Other scenario analyses may be proposed to support INESSS's evaluation of the efficiency of the product under evaluation. For example, these may be conducted by limiting the analysis to a subpopulation of the requested indication, by selecting other relevant comparators, or by applying specific reimbursement terms or uncertainty management approaches.

Comparators

Refer to Section 4.5 on relevant comparators.

Analysis perspective

The pharmacoeconomic analysis should take into account the two perspectives indicated below:

- the perspective of a public health and social services system (SSSS) in Quebec;
- societal perspective.

The first perspective considers only the direct effects and costs attributed to the health and social services system, while the second adds to the analysis the direct costs attributed to other payers and indirect costs—e.g., those incurred by patients or their caregivers, those associated with lost productivity, etc. Regarding effects other than those related to health and social services, this includes, among other things, the impacts of the intervention not directly linked to health, such as improved educational attainment, harm reduction, etc. If the societal perspective is not deemed relevant, briefly explain the reasons.

Sources of Inputs (Clinical, Economic, and Utility Values)

The sources of data on efficacy and safety should be the same as those supporting the assessment of the therapeutic value of the evaluation request. If this is not the case, a justification must be provided. When clinical studies used to assess therapeutic value constitute a valid source of data for the intended comparison, an analysis must at a minimum be conducted directly based on these results. Data from indirect comparisons may also serve as clinical inputs or be incorporated into scenario analyses. As a reminder, data from indirect comparisons, whether published or not, must be presented in the absence of a direct comparison between the subject under study and the relevant comparator(s). The assumptions used to extrapolate clinical data beyond the time horizon of the clinical study must be justified.

As for the various data sources used to calculate direct and indirect costs, they must originate from the Quebec context whenever possible, or from Canada, and costs must be presented in constant dollars for the current or previous year. For reference, certain sources are listed in Appendix VIII. Other sources may also be used.

With regard to utility values, which are central to cost-utility analyses, these may also come from various sources, and the chosen approach must be supported by a rationale. The INESSS guidelines on economic evaluations (INESSS, 2025) discuss best practices regarding utility in greater detail. A targeted literature review of the utility values published in the indication requested by the manufacturer is recommended. It should justify the approach chosen for including these inputs in the efficiency analysis. When values derived from clinical studies differ from those reported in the scientific literature, an explanation for these differences should be provided. Questionnaires and case studies, the data collection protocol, response rates, aggregated results with associated confidence intervals, and the methodology used to derive these values (including increments and decrements) must be made available to INESSS when available. Adjusting utility values according to Canadian or Quebec preferences should be considered.

Time Horizon and Discount Rate

The time horizon used in the analysis must be sufficiently long to account for all relevant effects and incremental costs between the subject under study and its comparator(s). When the duration exceeds one year, discounting must be applied beyond that year. A rate of 1.5% for costs and benefits must be used to determine the primary result. A rate of 3% may be used in sensitivity analysis. To ensure analytical consistency, the same time horizon is used for both costs and benefits.

Modeling and Analytical Methods

A comprehensive description of the model's structural aspects is required. A diagram illustrating the various health states and the relationships between them must support this description. All analytical methods supporting the modeling should be described, explained, and justified. For example: methods for handling biased, missing, or censored data; extrapolation methods, particularly for the long term; data combination methods; approaches for validating or adjusting a model; methods for managing heterogeneity and uncertainty; etc. The main assumptions of the analysis and its parameterization must be transparent, and its calculations simplified and disaggregated. These elements must also be easily modifiable by the user. Heterogeneity and parametric uncertainty must be sufficiently characterized in a way that is e . Finally, attention must be paid to the apparent, internal, and external validation (i.e., with respect to the requested indication and available data) of the model and its results; a section of the report must describe the validation procedures undertaken. Where appropriate, a table or figure showing the correspondence between the model outputs and the observed results of the clinical study should be provided.

When a clinical benefit is inferred (e.g., an overall survival benefit) but is not demonstrated by studies, the modeling must allow the user to derive this benefit. If this benefit is plausible, a rationale accompanied by indirect evidence must support this hypothesis. **This requirement also applies when the estimate of the clinical benefit is based on an intermediate parameter.**

In the specific case of survival analyses or analyses of time to event, at least six parametric distributions (exponential, Weibull, Gompertz, log-logistic, log-normal, generalized gamma) must be explored, and the choice of distribution must be justified and easily modifiable. To facilitate visual inspection, the results of the Kaplan-Meier estimator must be included in the provided Excel file and plotted on the same graph as the parametric distribution selected for the analysis. These parametric distributions must be accompanied by tests or analyses (the visual representation of cumulative risks on a logarithmic scale, the Grambsch and Terneau statistical test, and the Schoenfeld residuals test) to confirm or refute the hypothesis of proportionality of risks, as well as information criteria to assess the quality of the model fit. Visual inspection of this fit must also be possible. In the presence of immature clinical data, particular attention must be paid to the external validity of long-term results derived from extrapolation. It is recommended to support the plausibility of these results using other data sources.

The calculation of drug costs must be transparent, and its parameterization (e.g., dosage adjustments, treatment breaks, etc.) must be well-supported.

A table summarizing all parameters, assumptions, and values, as well as the distribution of the respective values selected, must be provided.

The INESSS guidelines on economic evaluations (INESSS, 2025) address best practices in modeling.

Outcome Measurement and Consequences of Uncertainty

In the case of a cost-utility analysis, the primary outcome ($/QALY gained, etc.) must be presented using a probabilistic approach, supplemented by a deterministic approach. If there is more than one relevant comparator, a sequential analysis, presented in tabular form in ascending order of costs, accompanied by a graph showing the efficiency frontier, should be preferred. For cost-minimization analyses, a probabilistic approach is recommended but not required.

Justification is required for the number of iterations used in the probabilistic analysis (e.g., through a convergence test that accounts for all relevant parameters) and for the cohort size in a microsimulation model. These values must be user-configurable. **The execution time should be reasonable within a 7-hour workday.** If a reasonable timeframe cannot be met, other open-source software may be used to perform the calculations (hybrid approach). The choice of distributions selected for each parameter must be explained. The use of a *random seed*—a sequence of pseudorandom numbers sometimes used to speed up the random sampling process—must be explained. If included in the analysis, the user must be able to modify or remove it without affecting the integrity of the analysis. Additionally, the values drawn for all efficacy and utility parameters must remain clinically plausible. In the specific case of analyses on survival or time to event, the inclusion of survival parameters in the probabilistic analysis is expected. These must account for the Cholesky decomposition.

The result should also be presented in a disaggregated manner, that is, broken down by its various components, in terms of health effects and cost categories, for both the subject

under study and its comparators. In the case of a cost-utility analysis, the “cost-effectiveness acceptance curve” and the “cost-effectiveness scatter plot” must be presented, along with the efficiency benchmarks at $50,000/QALY gained and $100,000/QALY gained. Univariate deterministic sensitivity analyses that characterize the consequences of uncertainty may accompany the results, for example in the form of a Tornado diagram. Scenario analyses addressing the key assumptions and choices underlying the analysis are expected, along with an assessment of the observed impact on the results.

APPENDIX III

Methodological aspects regarding the budgetary impact

Population, target market, and comparators

The target market in which the product under evaluation is positioned should include the comparator treatments administered to the population associated with the requested indication. If this positioning within the target market causes a shift in the use of these comparators over the time horizon—for example, to a later intent—this shift must be taken into account in the analysis. Finally, when the requested indication differs from that recognized by Health Canada, an alternative analysis, known as a scenario analysis, corresponding to the population targeted by Health Canada must also be submitted.

Time Horizon, Discounting, and Perspective

The budget impact analysis must be conducted over a 3-year time horizon, spread over 3 12-month periods following the potential listing of the drug, blood system product, or medical device related to drug administration. These results must not be discounted. The analysis is conducted from one of the following perspectives applicable to the subject under evaluation:

- The perspective of the public drug insurance plan and healthcare facilities – For drugs, supplies, or devices reimbursed by the RAMQ, the acquisition cost must be considered, based on the current guaranteed selling prices and, if appropriate, the costs of the pharmacist's professional services as well as the wholesaler's profit margin. For drugs, supplies, or devices reimbursed by healthcare facilities, only the acquisition cost is taken into account. If their acquisition or dispensing incurs additional costs for the facilities, particularly those caused by regulatory requirements or program fees, these must be included.
- The perspective of the Ministry of Health and Social Services – The acquisition cost of blood system products must be considered. In the event of a difference in administration methods resulting in higher or lower costs for healthcare facilities, these costs must also be included in the analysis.

For certain items under evaluation, the first two perspectives must be combined due to the interdependence of the markets affected by their listing. When warranted, a broader perspective may also be relevant to more accurately assess the magnitude of the budgetary burden on the system. This perspective may include one of those outlined above, supplemented by the inclusion of other costs, the RGAM perspective (i.e., including the budgetary impact on private insurers), or that of a health and social services system.

It should be noted that when a drug that can be administered in an outpatient setting is combined with a cancer treatment drug administered exclusively in a healthcare facility, the costs of the drug under evaluation must be allocated to the healthcare facility budget.

For more information, please refer to Circular 2000-028 from the Ministry of Health and Social Services (MSSS).

Market Size, Methodological Approaches, and Projections

One of the following two approaches, or a combination of both, is typically used to estimate market size in terms of prescriptions or units, or the number of people treated and to be treated: the approach based on billing or sales data for drugs, blood products, or medical devices related to drug administration, and the epidemiological approach.

The first is based on a model aimed at quantifying and projecting the number of units or prescriptions reimbursed or sold for listed or reimbursed comparator treatments. The second is based on a model that uses a set of parameters to define, most often in terms of patient numbers, the market targeted by the indication or recognized use. Market trends, distinguished based on whether the product under evaluation is listed or not, will depend on several factors; these must be described and referenced, and the analytical method and its calculations must be explained.

Market shares

Market share estimates reflect the assessed product's ability to become part of the therapeutic arsenal available to clinicians, that is, the proportion of its anticipated use for the targeted indication. These estimates must be clearly explained. It is recommended to describe the size and evolution of these market shares over the years. Various adjustments can be made in the analysis calculations to account for the gradual introduction of the evaluated product's use over time—e.g., the assumption that patient adoption occurs gradually, one month at a time, over the three 12-month periods. When multiple comparators are affected by its reimbursement, it is necessary to specify the proportions in which the market shares of the evaluated product will come from the different options over the entire time horizon of the analysis.

Costs of drugs, blood products, or medical devices related to drug administration

Various data sources used to calculate these costs are considered acceptable. These sources must provide costs specific to the Quebec context and present them in constant dollars for the current or previous year. These costs should account for anticipated durations of use in a real-world setting, particularly as estimated from billing data, results from clinical studies, or the submitted pharmacoeconomic analysis. The budget impact analysis must share the same set of clinical and economic assumptions as the pharmacoeconomic analysis.

Outcome Measurement and Consequences of Uncertainty

A table summarizing the main assumptions used in the analysis, including those for other options that support the sensitivity analyses, must be provided.

Depending on the perspective chosen and for the main analysis, if other health resources are affected by the listing of the drug, blood system product, or medical device related to the administration of an evaluated drug, their budgetary impact must be included in the results table provided. The impact must be broken down by the relevant budgets.

Companion Test

When a companion test is required, a budget impact analysis specific to that test must be submitted. This analysis must account for the expected new volume for this test, based on the platforms most likely to be used or implemented in Quebec. If a confirmatory test is required, its cost must also be considered. The weighted values listed in the appendix of the MSSS's Quebec Directory and Measurement System for Medical Laboratory Procedures may serve as a source of information for estimating these costs. To better understand the process for adding a new test to *the Quebec Directory and Measurement System for Medical Laboratory Procedures*, please consult the following link: Process for adding a new test to the Quebec Directory and Measurement System for Medical Laboratory Procedures.

APPENDIX IV

Standard values adopted by INESSS

Where applicable and by agreement, the weight and body surface area indicated below must be used. Subject to justification, different values may be used.

Target population (sex)	Body weight[a]	Body surface area[a]
Women/Men	77 kg	1,87 m^2
Women only	70 kg	1,74 m^2
Men only	84 kg	2,00 m^2
Infants and young children	On a case-by-case basis, depending on medical condition, age at diagnosis, and the timing of treatment initiation.	

a Although other characteristics of individuals exposed to the treatment influence the estimation of these average values, only age and sex were considered. These averages were estimated by the Institut national de santé publique du Québec (INSPQ) using data from the 2020–2021 Quebec Population Health Survey (EQSP) conducted by the Institut de la statistique du Québec (ISQ).

Wholesaler's profit margin and cost of the pharmacist's professional services

The calculation of drug costs must account for the wholesaler's profit margin and the cost of the pharmacist's professional services, where applicable. To this end, a profit margin of no more than 6.5% must be included. Regarding professional service fees, INESSS recommends using the "0-C" rate—that is, the rate for filling a prescription renewal (48,500 prescriptions or fewer) during the current year (or the most recent available) taken from the RAMQ *Pharmacists' Manual*—as an approximation of a monthly dispensing cost. Where relevant, other rates should be considered based on the product, such as for non-sterile compounded preparations, opioid substitution therapy, the prescription of a medication or the initiation of drug therapy, or parenteral therapies.

APPENDIX V

Real-world data

The following are examples of characteristics common to real-world data.

Data sources
Registers
Data collected as part of a randomized pragmatic trial
Medical-administrative databases
Electronic health records
Billing database

Methodological approaches	
Observational designs	Experimental designs
Cohort studies	Cluster-randomized trials
Case-control studies	Non-randomized comparative studies
Before-and-after studies	

Real-world studies can provide additional information to pivotal clinical trials or address uncertainties and concerns that exist or were raised by INESSS during a previous evaluation.

Along with these studies, the following items must be submitted:

- A description of the context for submitting real-world evidence;
    - A clear justification of the need to use real-world evidence and how the real-world evidence fits in compared to other submitted studies;
- A report containing the following information, as applicable based on the study protocols and data sources:
    - the research question;
    - the target population and its representativeness relative to the Quebec population;
    - the data source used;
    - a description and definition of key elements—such as measures of exposure and outcomes, and potential confounding factors;
    - inclusion and exclusion criteria;

- the characteristics of the included patients;
- the methodology describing how the data were collected, processed, transformed, and matched, if applicable;
- the statistical plan;
- sources of potential bias and how these biases were mitigated.

If certain information cannot be provided, a justification is required.

- Study protocol, published or unpublished, if available.

APPENDIX VI

Folder structure of a submission file

The following folder structure is a schematic example of an electronic file submitted for evaluation to INESSS. It is expected that multiple nested subfolders be avoided.

1 - Administrative

a. Cover Letter
b. *Drug Registration Application* Form
c. Notice of Compliance
d. Labels
e. Authorization to Share Information
f. Consent Form (if file is aligned)
g. Registration Status in Other Provinces (if required)
h. Form *Summary description of the case*

2 - Clinical

4. Published clinical studies or manuscript for publication
    i. Study AB003_Caron *et al*. 2024
    ii. Study AB002_Caron *et al*. 2022
    iii. Study AB001_Caron *et al*. 2021
    iv. Study CD001_Caron *et al*. 2019
    v. Indirect comparison
    vi. Full Clinical Study Report of the pivotal study (CSR)
        1. CSR_Study AB003
        2. CSR_Study AB003_Statistical Analysis Plan (SAP)
    vii. Other relevant publications (if applicable)
    b. Appendices, supplements, errata, or editorials
    c. Posters, abstracts, or oral presentations related to the main studies
        i. Caron 2022
        ii. Caron 2021
    d. List of published and unpublished clinical studies
    e. Clinical executive summary
    f. Detailed Summary – Clinical Studies Section (2.7.3)
    g. Health Canada Reviewers' Report
    h. Product Monograph

3 - Economic

a. Price Appropriateness

b. Pharmacoeconomic Study
    i. Analysis.pdf
    ii. PE.xls spreadsheet
        1. PE References
c. Budgetary impact
    i. Budgetary impact.pdf
    ii. Budgetary Impact.xls
        1. AIB references

4 - Additional Information

a. Health needs
b. Effects on public health
c. Effects on the health and social services system

APPENDIX VII

Proposed Template for an Indirect Comparison Report

The following template provides a schematic structure for drafting an indirect comparison report, to facilitate its analysis and interpretation. If another template is used, this information should ideally be included therein.

1- Objectives of the indirect comparison and rationale

2- Methods

a. Method used for the systematic literature review

i. Study selection criteria based on the PICOS approach

ii. Description of data sources

iii. Search strategy

iv. Process for selecting relevant studies

v. Data extraction

vi. Assessment of the methodological quality of the studies

b. Method used to assess the feasibility of the indirect comparison

i. Inclusion criteria for studies in the indirect comparison

- Type of population or subpopulation
- Type of intervention of interest and comparators selected
- *Outcomes of* interest
- Relevant data (e.g., effect size and 95% CI)

ii. Methods for identifying prognostic factors and potential effect modifiers

iii. Descriptive and comparative analysis of the studies included in the indirect comparison

c. Indirect comparison method

i. Network geometry of the indirect comparison

ii. Justification for the chosen indirect comparison method

iii. Hypotheses tested and statistical methods used to estimate the effects of interest *(efficacy, safety, effect on quality of life)*

iv. Methods for assessing and exploring heterogeneity and consistency (if applicable)

v. Method for handling missing data (if applicable)

vi. Sensitivity analyses for each parameter of interest

vii. Method for ranking interventions *(if more than two interventions are compared)*

3- Results

a. Results of the systematic literature review

i. Description of the results of the selection process, including the PRISMA 2020 flow diagram

ii. Overview of the characteristics of the selected studies (descriptive summary and table)

iii. Presentation of the results of the assessment of the methodological quality of the studies (descriptive summary and figure)

iv. Detailed search strategies (in the appendix)

b. Results of the assessment of the feasibility of the indirect comparison

i. Description of the studies selected for the indirect comparison *(number of studies, interventions, comparators, outcomes of interest, target population or subpopulation)*

ii. List of excluded studies and reasons for their exclusion

iii. List of relevant prognostic factors and effect modifiers selected

iv. Results of the descriptive comparative analysis of the selected studies *(summary and comparative table)*

v. Geometry of the selected intervention networks

c. Results of the main analysis and sensitivity analyses of the indirect comparison

i. Efficacy

ii. Safety

iii. Effect on quality of life

d. Results of quantified heterogeneity and subgroup analyses (if applicable)

i. Efficacy

ii. Safety

iii. Effect on quality of life

e. Inconsistency of results *(applicable to network meta-analyses only)*

f. Outcome of intervention ranking *(if more than two interventions are compared)*

4- Discussion

a. Summary of key findings
b. Description of the robustness of the main results
c. Methodological limitations of the analyses conducted and their potential impacts on the observed results

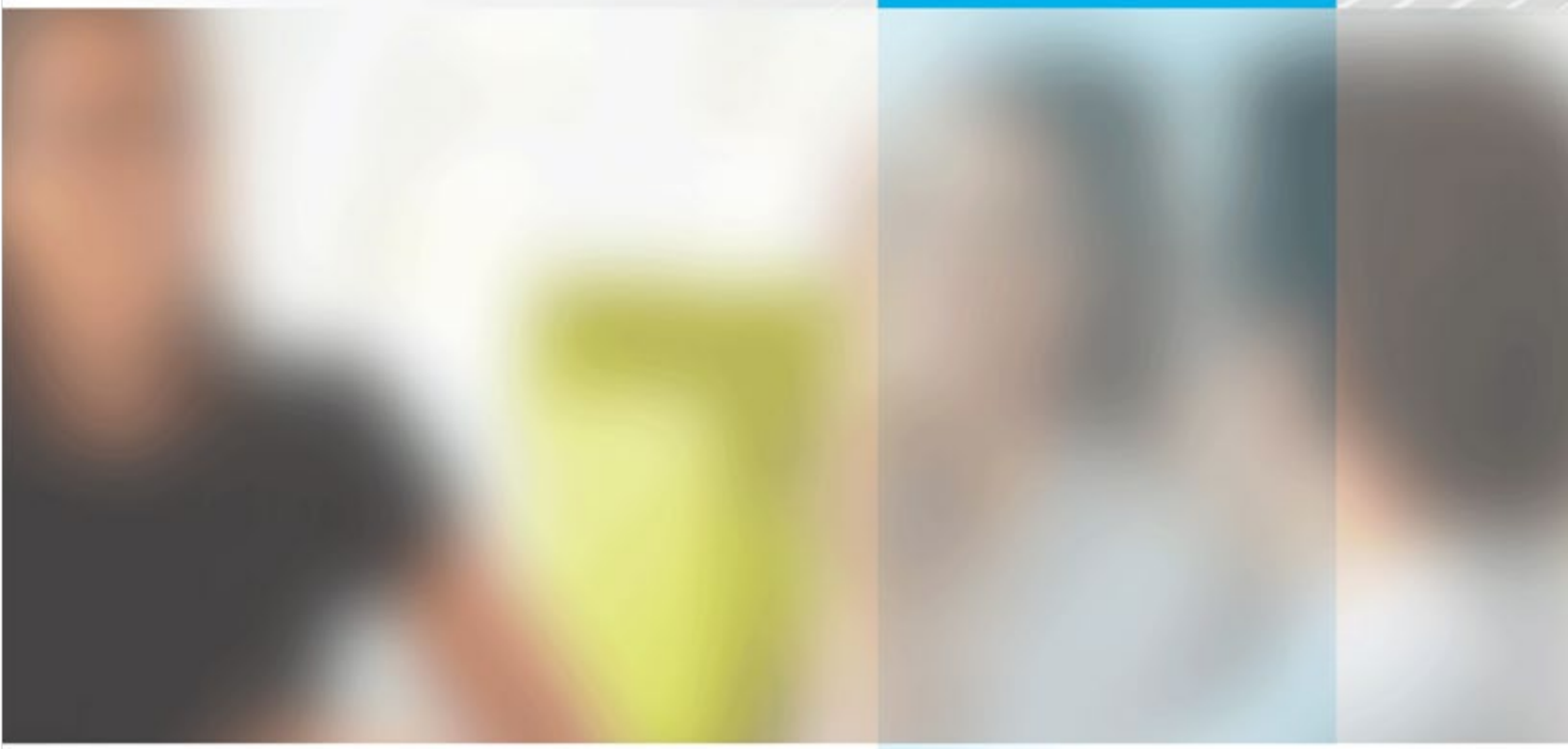
5- Conclusion

APPENDIX VIII

Sources of economic inputs

Reference	Summary description
Ministry of Health and Social Services (MSSS)	
Costs of short-termintensive care unit	Appendix II – Daily Rates: presents daily rates for short- and long-term care, as well as daily rates for rehabilitation centers, newborns, and youth services
Costs for laboratory tests	Presents the cost per weighted value (WV), which is the relative value associated with each procedure in the directory. It reflects the resources (human and material) required to perform a procedure
Unit values for estimating the technical and support components of medical tests and procedures	Compiles data used to estimate the costs of the technical and support components of certain procedures (to which fees are added, if applicable)
Outpatient service rates	Presents the rates for interprovincial/interterritorial reciprocal billing of outpatient services
Costs of bone marrow and stem cell transplants	Appendix III – Interprovincial Rates for Bone Marrow and Stem Cell Transplants
Costs for Organ Transplants	Rates for interprovincial billing of transplants designated as very costly, as well as the billing process
Annual Financial Report (Form AS-471)	Compiles quantitative financial and non-financial data by activity center
Quebec Health Insurance Board (RAMQ)	
List of medications	*List of medications* covered by the general drug insurance plan
Compensation for general practitioners	Fee-for-service, fixed-fee, retainer, hourly rate, *per diem*, and mixed payment methods
Remuneration of specialists	Fee-for-service, flat-fee, salaried, and mixed compensation
Manual of In-House Laboratory Services	In-House Laboratory Services Manual (SLE)

Pharmacists' Manual	Pharmacists' Manual and Pharmacists' Agreement
Costs of Certain Consultations and Medical Visits	Summary tables of billing codes and rates for Tab B – Consultation, Examination, and Visit
Funding for Family Medicine Groups (GMF) and Associated Costs	Funding and Professional Support Program for Family Medicine Groups.
Other sources	
AQPP Drug List	The AQPP drug list for all products available in Quebec, including those reimbursed by the RAMQ (Paid access)
Treasury Board	Salary scales for healthcare professionals
CIHI	Hospitalization Cost Estimates: CIHI's per-patient cost estimator allows users to estimate the average costs of various hospital services, with the option to filter data by province.
Quebec Institute of Statistics and Statistics Canada	Estimating Productivity Losses Due to Absenteeism or Presenteeism



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