Lot Release Program for Schedule D (biologic) drugs:

Revised guidance document for implementation

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Lignes directrices sur le Programme d'autorisation de mise en circulation des lots de drogues visées à l'annexe D (produits biologiques) : Lignes directrices révisées pour la mise en œuvre

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Foreword

Guidance documents are meant to provide assistance to industry and health care professionals on how to comply with governing statutes and regulations. They also provide guidance to Health Canada staff on how mandates and objectives should be met fairly, consistently and effectively.

Guidance documents are administrative, not legal, instruments. This means that flexibility can be applied. However, to be acceptable, alternate approaches to the principles and practices described in this document must be supported by adequate justification. They should be discussed in advance with the relevant program area to avoid the possible finding that applicable statutory or regulatory requirements have not been met.

As always, Health Canada reserves the right to request information or material, or define conditions not specifically described in this document, to help us adequately assess the safety, efficacy or quality of a therapeutic product. We are committed to ensuring that such requests are justifiable and that decisions are clearly documented.

This document should be read along with the relevant sections of the regulations and other applicable guidance documents.

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Introduction

Purpose

This document outlines the Lot Release Program for Schedule D (biologic) drugs. It also covers the extent of the review and testing of biologic drugs prior to their release for sale in Canada by the Biologic and Radiopharmaceutical Drugs Directorate (BRDD).

The Lot Release Program

When a biologic drug is placed in the Lot Release Program, each lot of the biologic drug is subject to the Lot Release Program before sale in Canada.

"Sell" as defined in the *Food and Drugs Act* includes offering for sale, exposing for sale, having in possession for sale or distributing to one or more persons, whether or not the distribution is made for consideration.

The program is risk-based and covers the pre- and post-market stages of a drug's lifecycle. Its authority comes from sections C.04.007, C.04.008 and subsection C.08.002(3) of the *Food and Drug Regulations* (regulations). The regulations give BRDD the regulatory authority to:

- examine information pertaining to representative lots of a biologic drug (as part of the new drug submission examination process) and to issue requests made pursuant to subsection C.08.002(3) of the regulations within that process **and**
- request lot documentation in accordance with section C.04.007

Products are assigned to one of four lot release evaluation groups. Each group has different levels of regulatory oversight (testing and/or documentation review) based on the degree of risk associated with the product. This graduated risk-based approach to testing and oversight means that BRDD can focus ongoing testing on products that require enhanced surveillance.

BRDD applies criteria to determine the appropriate evaluation group, including but not limited to the:

- nature of the product
- target population
- lot testing history
- manufacturer's production and testing history

For Groups 2 and 3 a formal release letter from BRDD is required before each lot is sold. For Groups 1A and 4, the sponsor notifies the BRDD through a notification process. The BRDD aims to respond to Group 1A and Group 4 notifications within 2 business days.

BRDD reassesses lot release activities on an ongoing basis. As the level of product oversight may change based on benefit and risk considerations, a product may be moved to a different evaluation group over its lifecycle.

Scope

This guidance document applies to all biologic drugs that the BRDD regulates.

Background

Biologic drugs are isolated from or manufactured using living organisms. For this reason, they are more variable than chemically synthesized drugs and require additional regulatory oversight.

The Lot Release Program provides an additional check on biologic drugs to help assure their safety for human use.

Abbreviations and acronyms

BRDD: Biologic and Radiopharmaceutical Drugs Directorate

CoA: certificate of analysis

CPID-B (Schedule D drugs): certified product information document-biologics

(Schedule D drugs)

CTA: clinical trial application

CTA-A: clinical trial application amendments

DIN: drug identification number

DIN-B: drug identification number-biologics (DIN-B drugs)

GMP: good manufacturing practices

HDE: human-derived excipient

MRA: mutual recognition agreement

NDS: new drug submission

NOC: notice of compliance

ORA: Office of Regulatory Affairs

SNDS: supplement to a new drug submission

Definitions

Aborted lot: Wherein a batch record is issued, for any step in the production of a bulk intermediate or final product, but the batch is not released due to a breakdown in the manufacturing process related to facility systems, equipment, or procedures.

Human-derived excipient: Any component of a drug product derived from a human source, other than the claimed therapeutic ingredient(s).

Lot documentation: Information submitted by the manufacturer to demonstrate the lot is suitable for sale in Canada. May include certificates of analysis, attestations and completed worksheets.

Lot failure: A drug substance or final product lot or batch that has been rejected because it has failed to meet in-process or final release specifications.

Manufacturer/Sponsor: For biologic products, the sponsor is whose name the drug submission is filed under. Where a drug identification number (DIN)/notice of compliance (NOC) is issued, the manufacturer is the company:

- in whose name the DIN/NOC is registered (the DIN/NOC holder) **and**
- whose name must be included on the product label and product monograph/package insert

For CTAs and CTA-As, sponsor is defined by Division 5, Part C of the regulations as the individual, corporate body, institution or organization that conducts a clinical trial.

Note that the sponsor is not necessarily the company that fabricates the drug product.

Pre-market testing: BRDD may perform laboratory testing during the review period on new drug submissions, supplements to new drug submissions (containing chemistry and manufacturing changes), or DIN-B applications. We usually test samples from 3 to 5 consecutively manufactured lots. We also assess the suitability or robustness of key release methods or reagents. A key release method is typically one that controls an attribute that impacts the quality, safety and /or efficacy of the product.

Reprocessing: Subjecting all or part of a batch or lot of an in-process drug, a bulk process intermediate (final biological bulk intermediate) or a bulk drug of a single batch/lot to a previous step in the validated manufacturing process due to failure to meet predetermined specifications. Reprocessing procedures are foreseen as occasionally necessary and are validated and pre-approved as part of the marketing authorization.

Reworking: Subjecting an in-process drug, a bulk process intermediate (final biological bulk intermediate), or final product of a single batch/lot to an alternate manufacturing

process due to a failure to meet predetermined specifications. Reworking is an unexpected occurrence and is not pre-approved as part of the marketing authorization.

Evaluation groups

Introduction

This section describes each of the evaluation groups in the Lot Release Program. After receiving the post-decision letter following a notice of compliance (NOC), no objection letter (NOL), or decision letter (DIN-B and Periodic Quality Reports), the sponsor should follow the process for the post-approval evaluation group assigned to the product.

In general, the BRDD communicates to the sponsor the outcome of testing and/or documentation review by letter. BRDD provides a release letter to the sponsor releasing the lot for sale in Canada. In certain situations, a notification process is used instead. Notifications are made by sponsors. A notification form submitted by the sponsor attests that all specifications have been met.

Refer to:

- Group 1A lot notification form
- Group 4 lot notification form

Group 1: Pre-approval stage

BRDD may assign biologic products under review as a clinical trial application (CTA), a new drug submission (NDS) a supplement to a new drug submission (SNDS) or a DIN-B submission to group 1.

Evaluation group 1 has two distinct sub-groups:

- Group 1A
- Group 1B

Group 1A: Clinical trial materials

Group 1A consists of clinical trial materials associated with authorized CTAs. BRDD limits the scope of notifications (formerly “fax-backs”) for Group 1A to products derived from human plasma or those containing human-derived excipients (HDEs). Albumin is an example.

Note: If a clinical trial product is out of specification, the sponsor should contact the Biologic and Radiopharmaceutical Drugs Directorate's Office of Regulatory Affairs (BRDD-ORA) immediately by email at brdd_faxback_dmbr@hc-sc.gc.ca.

Prophylactic vaccines

For prophylactic vaccines, BRDD may require the certificate of analysis (CoA) to be provided for each vaccine lot that is to be used in the clinical trial.

Where a CoA is required to be submitted, a formal release letter approving the sale of the lot in Canada is required from BRDD before use in the clinical trial. To assess whether a lot is suitable for sale, BRDD may request a sponsor to provide more information and/or samples for testing.

If the clinical trial vaccine lot is sourced directly from the Canadian market, the sponsor does not need a formal clinical trial release letter. BRDD has already authorized these vaccine lots for sale under the Lot Release Program.

Individual inquiries for the requirements of specific investigational clinical trial material should be made as early as possible in the review process.

Other biologics

"Other biologics" are clinical trial materials associated with authorized CTAs. Sponsors complete and file a Group 1A lot notification form for lots derived from human plasma or containing human-derived excipients, such as albumin. Before using the lot in the related clinical trial, the sponsor must send in the completed Group 1A lot notification form. The sponsor must wait for a signed response from BRDD before using the lot in the clinical trial.

If the clinical trial material is a marketed product sourced directly from the Canadian market, the sponsor does not need to submit a Group 1A lot notification form. BRDD has already authorized these lots under the Lot Release Program.

Foreign marketed products

If the clinical trial material is a marketed product sourced from a foreign market, the sponsor is required to submit a Group 1A lot notification form if the product:

- is derived from human plasma **or**
- contains human-derived excipients, such as albumin

Group 1B: Pre-market testing

Group 1B is for samples associated with an NDS, an SNDS or a DIN-B that BRDD has requested.

BRDD generally tests samples from 3 to 5 consecutively manufactured lots to:

- ensure the manufacturing process is consistent
- assess the suitability or robustness of the key release methods

These lots may be released for sale in Canada once BRDD has granted market authorization. Sponsors must follow the requirements for the assigned evaluation group post-authorization.

Groups 2 to 4: Post-approval stage

Evaluation groups 2 to 4 apply to biologic products for which an approval letter has been issued.

Group 2: Sample testing and documentation review

Products requiring the highest level of assessment after a market authorization has been issued are assigned to Group 2. BRDD performs targeted testing and reviews lot documentation for products in this group.

A formal release letter which approves the sale of the lot in Canada is required from BRDD before each lot is sold. For Group 2, the targeted timeframe for a BRDD release decision is 6 weeks after receipt of all required information and samples.

The timeframe for some products may be longer, such as those with long bioassays.

BRDD may grant expedited release in special cases and if justified (such as a documented product shortage in Canada).

Group 3: Documentation review and periodic testing

Products requiring a moderate level of assessment after a market authorization has been issued are assigned to Group 3.

A formal release letter which approves the sale of the lot in Canada is required from BRDD before each lot is sold. For Group 3, BRDD reviews lot documentation, but samples are not routinely submitted by the manufacturer. However, BRDD may request samples from time to time for targeted testing.

Once BRDD receives all the required information, it usually takes 2 weeks to make a release decision for products in this group. If BRDD requested samples, the timeframe to make a release decision is 6 weeks.

BRDD may grant expedited release in special cases and if justified.

Group 4: Notification and periodic testing

Products in Group 4 do not undergo sample testing or documentation review. However, BRDD may conduct periodic testing and/or request to review documentation.

When a biologic drug is assigned to Group 4, the manufacturer of that drug must notify BRDD when a lot containing human-derived excipient(s) is to be sold in Canada. To do so, use the Group 4 lot notification form. The manufacturer must wait for a signed response from BRDD prior to use of the lot.

Factors for assignment of evaluation group

BRDD generally considers a number of factors when assigning a drug product to an evaluation group, including the following:

Product indication: The degree of oversight that is applied to a biologic drug depends on its indication and risk-benefit assessment, with consideration given to:

- age of target population
  - for example, infants and seniors
- disease state being treated
  - for example, life-threatening, acute, chronic
- duration of treatment
  - for example, short- or long-term
- objective
  - for example, treatment versus prophylaxis, replacement or diagnostic
- population size
  - for example, limited or widespread use

Nature of the product: All biologic drugs are assessed as to their nature, with consideration given to:

- source and level of control of the raw materials
- biochemical complexity of the drug product
- biochemical complexity of the drug substance
- complexity, robustness and level of control of the manufacturing process

- reliability and complexity of the methods used to evaluate identity, purity and potency of the drug substance and of the drug product

Production history:

- consistency of manufacturing
    - ability to manufacture a product with consistent quality, using the approved manufacturing process
- informed by the testing history
- informed by process changes or quality control strategy

Lot failures and aborted lots:

- information on the incidence of lot failures
- the severity of the cause for aborting a lot during production

Reprocessed lots:

- changes in the incidence and extent of reprocessing
    - an indication of the degree of control in the manufacturing process

Site history:

- quality and safety issues found during on-site evaluations and GMP inspections

Testing history:

- test results submitted by or for the manufacturer
- test results obtained by BRDD
- additional data derived from a review of lot documentation during inspection and inspection reports exchanged through mutual recognition agreements (MRA) and other sources
- the rate of re-test due to test failures and invalid tests

Post-market safety profile:

- product complaints
- adverse drug reaction reports
- product recalls and withdrawals

Movement between evaluation groups

After all of the factors have been considered, the BRDD assigns a product to an evaluation group.

Group assignment is reviewed on an ongoing basis. If the level of product oversight changes based on risk-benefit considerations, BRDD will assign the product to a different evaluation group. This may happen a number of times over the product's lifecycle. This approach supports a philosophy based on product maturity and periodic re-evaluation of product history.

Movement through evaluation groups may go up or down group levels (bi-directional). For example:

- quality issues detected by periodic testing during evaluation Groups 3 and 4 may cause the product to be reassigned to Group 2 or 3, until there is sufficient evidence available to support reassignment
- a subset of lots manufactured in a new facility may be in one evaluation group while another subset of lots of the same product may be in another group

BRDD may reassign a product to a different evaluation group at any time, including:

- following periodic assessment by BRDD
- after reviewing a periodic quality report
- in response to post-market information
    - as part of a submission review, routine inspection or in response to other sources

Testing categories for evaluation groups

The BRDD conducts both targeted and periodic testing.

Targeted testing for group 2

Targeted testing for Group 2 products specifies a combination of one or more assays for a particular biologic product. It may include a subset of tests ranging from 1 to the complete set of assays proposed by the manufacturer in the CTA, NDS, SNDS or DIN-B.

Routine lot release testing may be restricted to those critical assays in which failure to meet approved specifications may reflect product quality or safety.

The targeted testing regime is based on:

- BRDD's experience with testing of the product and results of testing of consistency lots and/or clinical trial materials
- lot failure information provided by the manufacturer
- other pertinent information such as information obtained from other regulatory agencies, product recalls and adverse drug reaction reports
- product stability profile and shelf life

Concurrent testing by BRDD and the manufacturer will be considered for products that require lengthy release tests, such as:

- cell enumeration tests for live, slow growing bacterial products
- cell culture infectivity tests for live viral vaccines

For concurrent testing, the manufacturer must promptly notify BRDD of any testing failures.

Periodic testing

Products in evaluation Groups 3 and 4 are subject to periodic testing. BRDD may ask for lot samples for periodic testing to confirm that the product meets specifications. Lot samples are selected based on risk assessment of factors such as production history, site history, testing history and other related factors.

Regulatory requirements for authorized biologic drugs

Sponsor/manufacturer information and regulatory requirements

Under section C.04.007 of the regulations, on request by BRDD the regulated party must provide information, samples or materials supporting lot release. The information requirements for the different evaluation groups are summarized in the summary of requirements for evaluation groups.

Under section C.04.008 of the regulations a Periodic Quality Report (PQR) may be required for biologic products with a DIN.

The periodic quality reporting frequency is on an annual basis or longer, as specified by the Minister. The requirements may vary depending on the product. BRDD will communicate this to the manufacturer. The factors considered include nature of the

product, product lifecycle stage, production history, site history, testing history, and post-market safety profile.

BRDD uses information from the PQR to confirm or reassign to the appropriate lot release category. BRDD may use information from the PQR to verify the consistency of the process, assess the ongoing safety and quality of the product, and highlight any trends. We may also use this information when deciding whether a product should be reassigned to a different evaluation group.

A PQR is also useful for providing regulatory context when:

- only a few lots produced in a facility are released in Canada **or**
- post-NOC changes are filed infrequently

Periodic quality reporting

We recommend that you use Health Canada's PQR template to provide periodic quality reporting information:

- Periodic quality report template

As an alternative, you may submit a report prepared for another competent regulatory authority that has similar information as the PQR. If you do, ensure it is updated with Canadian-specific information that includes:

- information in the PQR template
- lots sold in Canada, including lot numbers

In some cases, the PQR may be for more than one product under the same DIN holder.

Submitting the Periodic Quality Report

Refer to the following guidance document when preparing the PQR:

- Preparation of drug regulatory activities in the electronic common technical document format

You may coordinate the date of submission with BRDD to coincide with the submission of a similar report to another regulatory authority.

You may submit scientifically justified groupings of similar products (for example, related products where the trade names represent different strengths or presentations) as a single PQR. Send any questions about groupings to our Office of Regulatory Affairs.

If no lots are sold or manufactured for Canada or no lots are sold or produced internationally, the manufacturer should submit the PQR indicating this.

If the DIN has not been cancelled, then the manufacturer should submit a PQR, unless the periodic quality reporting requirement does not apply.

You should also include a copy of the regulatory enrolment process (REP) regulatory transaction (RT) template and product information (PI) template with the PQR.

During our review of the PQR, we may ask you to clarify or provide additional information via Clarification Request (with a 30-day target).

There is no approval letter or decision letter issued following review of the PQR. BRDD will notify the manufacturer if there is a change resulting from our review of the PQR, such as:

- an approved CPID-B
- feedback to provide to the manufacturer **and/or**
- a change to the lot release evaluation group for the product

Products derived from human plasma or containing human-derived excipients

For biologic drugs derived from human plasma or those containing human-derived excipients (HDE), the manufacturer/sponsor shall maintain a traceable link between:

- the drug product and the lot number(s) of the human plasma **and/or**
- the HDE used for the drug product lot

The manufacturer/sponsor must provide the lot number, manufacturer and other pertinent human plasma or HDE information:

- as part of the documentation for the lot release of products in evaluation groups 2 and 3 **or**
- using a Group 4 lot notification form at the time of sale in Canada for products in evaluation Group 4 containing HDE

Products in evaluation Group 1A derived from human plasma or those containing HDE must be supported by a Group 1A lot notification form.

All HDEs must meet the regulatory requirements for approval of HDEs as specified by BRDD. The manufacturer/sponsor should appropriately file any changes to the manufacturing of HDEs to BRDD.

Reassessment

Once a product has been assigned to an evaluation group, sponsors may request a reassessment by writing to the Office of Regulatory Affairs.

You may also send any requests to have a product reassigned to another evaluation group to the Office of Regulatory Affairs.

Contact us

If you have any questions or need more information about this guidance, contact:

Office of Regulatory Affairs
Biologic and Radiopharmaceutical Drugs Directorate
Health Products and Food Branch
Health Canada
100 Eglantine Driveway, Tunney's Pasture
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Ottawa ON K1A 0K9

E-mail: brdd.ora@hc-sc.gc.ca

Appendix: Summary of requirements for evaluation groups

Table 1: Summary of requirements for evaluation groups

Evaluation Group	Group 1A	Group 1B	Group 2	Group 3	Group 4
Evaluation group description	**Pre-approval** Clinical trials	**Pre-approval** Associated with NDS or SNDS and DIN-B submissions	**Post-approval** Products requiring the highest level of assessment	**Post-approval** Products requiring a moderate level of assessment	**Post-approval** Products requiring a low level of assessment
Sample requirements	**Prophylactic vaccines:** Samples of lots along with materials for testing samples (if necessary) may be requested **Other biologics:** No samples required	Generally, samples from 3 to 5 consecutively manufactured lots along with materials for pre-market testing of samples (if necessary) are submitted to BRDD for pre-market testing	Targeted testing (mandatory submission of samples of all lots to BRDD for testing) Materials for testing samples may also be requested	Products in group 3 are subject to periodic testing	Products in group 4 are subject to periodic testing upon request

Evaluation Group	Group 1A	Group 1B	Group 2	Group 3	Group 4
Document requirements	**Prophylactic vaccines:** Upon BRDD request, submit lot documentation for review **Other biologics:** Complete and file a Group 1A lot notification form for products derived from human plasma or those containing HDEs	Submit lot documentation for review	Submit lot documentation for review	Submit lot documentation for review	Group 4 Lot Notification form with lot number of product before each lot is sold in Canada for products containing HDEs, plus information on the HDE lot(s)
Approval mechanism	**Prophylactic vaccines:** If lot documentation has been requested, a written approval in the form of a release letter from BRDD is required	Upon request, lots from which samples were submitted for pre-market testing may be released for sale in Canada once an NOC or DIN-B is issued	A written approval for sale in the form of a release letter is required for all lots	A written approval for sale in the form of a release letter is required for all lots	A signed response from BRDD before each lot is sold in Canada for products containing HDEs

Evaluation Group	Group 1A	Group 1B	Group 2	Group 3	Group 4
	Other biologics: The sponsor must send in the Group 1A notification for products derived from human plasma or those containing HDEs before using the lot in the related Clinical Trial	The requirements will be that of the post-market evaluation group the product is assigned to			
Target timeline	Group 1A lot notification: The sponsor waits for a signed response from BRDD before using the lot in a clinical trial Within 2 business days	Not applicable	6 weeks after all required information and samples received May grant expedited release in special cases and upon appropriate justification, such as a documented product shortage in Canada	2 weeks after all required information received 6 weeks if periodic testing samples requested	6 weeks if periodic testing samples requested by BRDD Otherwise, within 2 business days

Evaluation Group	Group 1A	Group 1B	Group 2	Group 3	Group 4
Reporting requirements	Not applicable	Not applicable	BRDD may communicate to the manufacturer at approval/post approval, on a product-by-product basis, the requirement on an annual basis or at any longer interval for a Periodic Quality Report	BRDD may communicate to the manufacturer at approval/post approval, on a product-by-product basis, the requirement on an annual basis or at any longer interval for a Periodic Quality Report	BRDD may communicate to the manufacturer at approval/post approval, on a product-by-product basis, the requirement on an annual basis or at any longer interval for a Periodic Quality Report