

# **GUIDANCE FOR SPONSORS**

## Lot Release Program for Schedule D (Biologic) Drugs

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**Health Products and Food Branch**

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*Également disponible en français sous le titre: Ligne directrice à l'intention des promoteurs: Programme d'Autorisation de Mise en Circulation des Lots de Drogues Visées à l'Annexe D (Produits Biologiques)*

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## FOREWORD

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

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

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

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

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## 1.0 INTRODUCTION

### 1.1 Purpose

The purpose of this document is to outline the Lot Release Program for Schedule D (biologic) drugs and the extent of the review and testing of biologic drugs prior to their release for sale in Canada by the Biologics and Genetic Therapies Directorate (BGTD).

### 1.2 The Lot Release Program

Each lot of a Schedule D (biologic) drug is subject to the Lot Release Program before sale<sup>1</sup> in Canada. The risk-based Lot Release Program covers both pre- and post-market stages. The Lot Release Program derives its legislative authority from section C.04.015 of the *Food and Drug Regulations*<sup>2</sup>. Products are assigned to one of four Evaluation Groups, with each group having different levels of regulatory oversight (testing and/or protocol review) based on the degree of risk associated with the product. The graduated risk-based approach to testing and oversight allows BGTD to focus ongoing testing on products for which enhanced surveillance is indicated such as vaccines and blood products. The criteria used to determine the appropriate Evaluation Group include, but are not limited to, the nature of the product, the target population, the lot testing history in BGTD, and the manufacturer's production and testing history.

In general, the outcome of testing and/or protocol review is communicated to the manufacturer via a Release Letter prior to the product's release for sale in Canada. In certain situations, a Fax-back process is used. A Fax-back form (Appendix I) which is submitted by the manufacturer<sup>3</sup> attests that all specifications have been met; receipt is acknowledged by Fax-back within 48 hours.

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<sup>1</sup> "Sell" includes offer for sale, expose for sale, have in possession for sale and distribute, whether or not the distribution is made for consideration.

<sup>2</sup> C.04.015 On written request from the Director, every fabricator, packager/ labeller, tester, distributor referred to in paragraph C.01A.003(b) and importer of a drug shall submit protocols of tests together with samples of any lot of the drug before it is sold, and no person shall sell any lot of that drug if the protocol or sample fails to meet the requirements of these Regulations

C.01A.003 b) a distributor of a drug for which that distributor holds the drug identification number.

<sup>3</sup> "Manufacturer" refers to the person in Canada responsible for the sale of the drug which may include, but is not limited to, the establishment licence holder, fabricator, DIN holder, and/or distributor of a drug for which that distributor holds the DIN.

### 1.3 Scope

1.3.1 This guidance document is applicable to all Schedule D (biologic) drugs regulated by BGTD.

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

### 1.4 Abbreviations, Acronyms, and Definitions

#### 1.4.1 Abbreviations and Acronyms

BGTD	Biologics and Genetic Therapies Directorate
CBE	Centre for Biologics Evaluation
CERB	Centre for Evaluation of Radiopharmaceuticals and Biotherapeutics
CoA	Certificate of Analysis
CPID	Certified Product Information Document
CTA	Clinical Trial Application
DIN	Drug Identification Number
GMP	Good Manufacturing Practices
HDE	Human-derived Excipient
MRA	Mutual Recognition Agreement
NDS	New Drug Submission
NOC	Notice of Compliance
RAD	Regulatory Affairs Division
S/NDS	Supplemental New Drug Submission
YBPR	Yearly Biologic Product Report

#### 1.4.2 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.

##### *Consistency Testing*

Laboratory testing performed by BGTD during the review period for New Drug Submissions or Supplemental New Drug Submissions. Generally, samples from 3 to 5 consecutively manufactured lots are tested.

*Human-derived Excipient*

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

*Lot Failure*

A drug substance or final product lot or batch that has been rejected due to failure to meet in-process or final release specifications.

*Protocol of Tests*

Information submitted by the manufacturer required to demonstrate that the lot is acceptable for sale in Canada. This may include Certificates of Analysis, attestations, and completed worksheets.

*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.

*Yearly Biologic Product Report*

A report required every year for all approved Schedule D (biologic) drugs.

## **2.0 EVALUATION GROUPS**

### **2.1 Group 1: Pre-Approval Stage**

All products under review as a Clinical Trial Application (CTA), or New Drug Submission (NDS), and in some cases a Supplementary New Drug Submission (S/NDS), are assigned to Evaluation Group 1 during the review period. Group 1 has two distinct sub-groups.

#### **2.1.1 Group 1A: Clinical Trial Materials**

This Evaluation Group consists of clinical trial materials associated with authorized CTAs. Sponsors are required to complete and file a Fax-back form (Appendix IA) and await a signed response from BGTD prior to use of the clinical trial material. For prophylactic vaccines,

BGTD issues a formal release letter for use of the vaccine lot in the clinical trial; the protocol of tests and usually samples are required to be submitted to BGTD.

### **2.1.2 Group 1B: Consistency Testing**

This Evaluation Group is intended for consistency samples associated with an NDS or S/NDS. Generally, samples from 3 to 5 consecutively manufactured lots are tested by BGTD to ensure consistency of the manufacturing process. Upon request, consistency lots may be released for sale in Canada once an NOC is issued; a formal release letter is required from BGTD.

## **2.2 Group 2 to 4: Post-Approval Stage**

Evaluation Groups 2 to 4 apply to biologic products for which an NOC has been issued.

### **2.2.1 Group 2: Sample Testing and Protocol Review**

Products requiring the highest level of assessment after issuance of an NOC are assigned to this Evaluation Group. Products in this group are subjected to Targeted Testing (Appendix II). A formal Release Letter which approves the sale of the lot in Canada is required from BGTD before each lot is sold. The targeted timeframe for products in this Group to be released is 6 weeks after receipt of all required information and samples. The timeframe for some products, such as those with long bioassays, may be longer. Expedited release may be granted in exceptional cases and upon appropriate justification (such as product shortage in Canada).

### **2.2.2 Group 3: Protocol Review and Periodic Testing**

Products requiring a moderate level of assessment after issuance of an NOC are assigned to this Evaluation Group. A formal Release Letter which approves the sale of the lot in Canada is required from BGTD before each lot is sold. For products in this Group, BGTD reviews testing protocols but samples are not routinely submitted by the manufacturer for Targeted Testing. Instead, at the discretion of BGTD, samples may be requested for Periodic Testing (Appendix III). The targeted timeframe for products in this Group to be released for sale is two weeks from the date that all required information is received.

### **2.2.3 Group 4: Notification and Periodic Testing**

Products in this Evaluation Group do not undergo sample testing or protocol review by BGTD. When a Schedule D (biologic) drug has been assigned to Evaluation Group 4, the manufacturer of that drug is required to notify BGTD via Fax-back (Appendix I) when a lot is to be sold in Canada. A Release Letter is not required prior to sale. At the discretion of BGTD, products in Evaluation Group 4 may also be subjected to Periodic Testing (Appendix III).



### **3.0 FACTORS CONSIDERED DURING ASSIGNMENT OF PRODUCTS TO EVALUATION GROUPS**

The factors considered when assigning products to Evaluation Groups are outlined in sections 3.1 to 3.6.

#### **3.1 Product Indication**

The degree of oversight to which a Schedule D (biologic) drug is subjected to during Lot Release is associated with its indication and risk/benefit assessment. Considerations include the following:

- age of target population (e.g. infants, seniors etc.)
- disease state being treated (e.g. life threatening, acute, chronic)
- duration of treatment (e.g. short/long term)
- health status (e.g. incurable, healthy)
- objective (e.g. treatment vs prevention vs replacement vs diagnostic)
- population size (limited/widespread use)

#### **3.2 Nature of the Product**

All Schedule D (biologic) drugs are assessed as to their nature, which is a consideration for Evaluation Group assignment. Considerations in evaluating the nature of the product include the following:

- source and level of control of the raw materials
- complexity, robustness and level of control of the manufacturing process
- chemical complexity of the drug substance
- chemical complexity of the drug product
- reliability and complexity of the methods used to evaluate identity, purity, and potency of the drug substance and the drug product

#### **3.3 Production History**

Consistency of manufacturing and the ability to consistently produce a drug without reworking is a consideration in the assignment of products to Evaluation Groups.

##### **3.3.1 Lot Failures and Aborted Lots**

Information on the incidence of lot failures and severity of cause of aborting a lot during production contributes to the assignment of a product to an Evaluation Group.

##### **3.3.2 Reprocessed Lots**

Changes in the incidence and extent of reprocessing are an indication of the degree of control in the manufacturing process and contributes to the information used for the assignment of products to Evaluation Groups.

### **3.4 Inspection History**

Quality and safety issues found during On-Site Evaluations and other inspections contribute to the assignment of products to the Evaluation Groups.

### **3.5 Testing History**

The test results submitted by or for the manufacturer, as well as test results obtained by BGTD are also part of the considerations used in assigning products to an Evaluation Group. Additional data may be derived from test protocol review during inspection and the exchange of inspection reports through Mutual Recognition Agreements (MRA), and other sources. In addition to actual test results, the rate of re-test due to test failures and invalid tests is also considered.

### **3.6 Post-market Experience**

Information from adverse drug reaction reports, product complaints, product recalls, and withdrawals contribute to the post-market safety profile of the drug product. This information is also used in the assignment of products to Evaluation Groups.

## **4.0 MOVEMENT BETWEEN EVALUATION GROUPS**

The initial assignment of a product to an Evaluation Group upon receiving approval is at the discretion of BGTD, taking into account considerations outlined in Section 3. Usually, with the exception of vaccines which may remain in Evaluation Group 2 indefinitely, products assigned to Evaluation Group 2 remain in that group for a period of one year, or until such time as five lots have been tested and released, whichever is longest. Following the one year or period where five lots have been tested satisfactorily, the product may be re-assigned into Evaluation Group 3 or 4 providing there have been consistent and reliable testing outcomes observed while in Group 2 and that there have been no changes in the manufacturing process that may have an impact on the quality of the drug.

Products that are produced from well controlled raw materials through reliable and consistent processes, and that can be readily assessed with respect to identity, purity and potency through reliable test protocols may be assigned to Evaluation Group 4 at the time of approval.

Movement through the Evaluation Groups may be bi-directional. For example, quality issues detected by Periodic Testing during Evaluation Groups 3 and 4 may result in product re-assignment to Group 2 or 3 until such time that sufficient evidence to support re-assignment of the product is available. Information obtained during routine inspections or from other sources may also affect the Evaluation Group assignment.

Re-assignment of a product to a different Evaluation Group occurs in one of two ways:

- 1) Upon review of the Yearly Biologic Product Report, manufacturers are notified if the product

is re-assigned to a different Group. The manufacturer may appeal within 60 days of notification, extensions may be given on a case-by-case basis upon request by the manufacturer, see Section 7.0.

- 2) Manufacturers may apply for re-assignment, in writing and provide the data outlined in Section 5.1 to the Director of CBE or CERB in order to be assessed for re-assignment into a different Evaluation Group.

## 5.0 SPONSOR INFORMATION AND REGULATORY REQUIREMENTS

Under section C.04.015<sup>1</sup> of the *Food and Drug Regulations*, the manufacturer shall provide information supporting Lot Release. A summary of the information requirements for the different Evaluation Groups is provided in Appendix IV.

Manufacturers of Schedule D (biologic) drugs in Evaluation Groups 2, 3, and 4 shall provide, under section C.01.014.5<sup>4</sup>, C08.007<sup>5</sup> and/or C.08.008 of the *Food and Drug Regulations*, information annually to Health Canada (BGTD). For the Lot Release Program, a Yearly Biologic Product Report (YBPR) is required (See section 5.1). Information from the YBPR may be used to verify the consistency of the process, to assess the on-going safety and quality of the product, and to highlight any trends. The information may also be part of the consideration of re-assignment of a product into a different Evaluation Group.

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<sup>4</sup> Every manufacturer of a drug shall, annually before the first day of October and in a form authorized by the Director, furnish the Director with a notification signed by the manufacturer or by a person authorized to sign on his behalf, confirming that all the information previously supplied by the manufacturer with respect to that drug is correct.

<sup>5</sup> Where a manufacturer has received a notice of compliance issued in respect of a New Drug Submission or Abbreviated New Drug Submission or a supplement to either submission, the manufacturer shall establish and maintain records, in a manner that enables an audit to be made, respecting

- a) animal or clinical experience, studies, investigations and tests conducted by the manufacturer or reported to him by any person concerning that new drug;
- b) reports from the scientific literature or the bibliography there from that are available to him concerning that new drug;
- c) experience, investigations, studies and tests involving the chemical or physical properties or any other properties of that new drug;
- d) any substitution of another substance for that new drug or any mixing of another substance with that new drug;
- e) any error in the labelling of that new drug or in the use of the labels designed for that new drug;
- f) any bacteriological or any significant chemical or physical or other change or deterioration in any lot of that new drug;
- g) any failure of one or more distributed lots of the new drug to meet the specifications established for that new drug in the submission or supplement; and
- (h) any unusual failure in efficacy of that new drug.

## 5.1 Yearly Biologic Product Report

5.1.1 The following information should be part of the YBPR:

5.1.1.1 Production information on both drug substance and drug product lots:

- number of lots produced for or sold on the Canadian market
- number of lots produced or sold internationally, from facilities licensed to produce lots for Canada
- number of lots reprocessed from facilities licensed to produce lots for Canada
- a review of all commercial lots intended for Canadian and international use that failed to meet established specifications, or were aborted due to manufacturing process failures, including those having been determined as having failed through studies, investigations and tests conducted by the manufacturer or reported to him by any person
- a review of all changes carried out to the process or analytic methods
- a concise, high-level review of critical deviations or non-conformances, related investigations, and resolution/corrective actions
- a list of changes to raw material suppliers and changes to non-compendial specifications

5.1.1.2 Information on drug substance and drug product test methods:

- frequency of retesting due to out-of-specification, including clarification on the reason for retesting
- frequency of invalid tests for stability-indicating test methods

5.1.1.3 Information on drug substance and drug product test results:

- a review of critical in-process controls and finished product results
- trend analysis for stability-indicating test methods
- a review of results of ongoing stability program(s)

5.1.1.4 Facility information:

- a review of regulatory actions taken by competent authorities that affect GMP status

5.1.1.5 Analysis of Adverse Drug Reaction Reports (Canadian and International) received by the manufacturer attributable to product quality

5.1.1.6 All product recalls including the reason for the recall and a summary of any corrective actions taken

5.1.1.7 If changes affecting the CPID have been made, an updated CPID (annotated and non-annotated, hard copy and electronic) is to be provided with the YBPR

### 5.1.2 Submission of Yearly Biologic Product Report

A report prepared for another competent regulatory authority that contains the information outlined in sections 5.1.1.1 to 5.1.1.7 may be updated with Canadian-specific information and submitted as the YBPR.

The YBPR should be submitted as an Addendum to the Annual Drug Notification Report no later than October of each year.

Alternatively, the date of first submission may be negotiated with BGTD, after which subsequent reports will be submitted every 12 months to the Regulatory Affairs Division (RAD).

## 6.0 HUMAN-DERIVED EXCIPIENTS

For Schedule D (biologic) drugs containing human-derived excipients (HDE), the sponsor shall maintain a traceable link between the drug product and the lot number(s) of the HDE used for the drug product lot<sup>6</sup>.

The lot number, manufacturer, and other pertinent HDE information must be provided as part of the documentation for the lot for release of products in Evaluation Groups 2 and 3, or via a Fax-back form at time of sale in Canada for products in Evaluation Group 4.

Products in Evaluation Group 1A formulated with HDE must be supported by CTA Fax-back forms.

All HDE used as excipients must meet the regulatory requirements for approval of HDEs as specified by BGTD. Any changes to the manufacturing of HDEs should be appropriately filed to BGTD.

## 7.0 APPEALS

Upon the assignment of a product into an Evaluation Group, manufacturers may appeal the grouping of their product in writing to the Director of CBE or CERB. BGTD will target 60 calendar days to assess the submitted information and provide a written response to the

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<sup>6</sup> Interpretation 11 of regulations C.02.011 and C.02.012 as outlined in the *GMP Annex for Schedule D drugs, Part 1*, indicates that "Batch records must document all biological starting materials and in-process materials used, in addition to all relevant test results."

manufacturer. Similarly, requests for re-assignment to another Evaluation Group should be directed to the Director of CBE or CERB.

## **8.0 EFFECTIVE DATE**

This Guidance document is effective as of June 1, 2005.

The requirements for sponsors to submit YBPRs and to notify BGTD via Fax-back for all Group 4 products become effective June 1, 2006. Until then, the Fax-back process for Group 4 products will continue to apply only to those products that contain HDE.

## **9.0 ADDITIONAL INFORMATION**

If you have any questions or require information regarding this guidance, contact:

Regulatory Affairs Division  
Centre for Policy and Regulatory Affairs  
Biologics and Genetic Therapies Directorate  
Telephone: (613) 957-1722  
Fax: (613) 941-1708  
E-mail: [BGTD\\_RAD\\_Enquiries@hc-sc.gc.ca](mailto:BGTD_RAD_Enquiries@hc-sc.gc.ca)

**APPENDIX IA**

CTA FAX-BACK FORM  
**CLINICAL TRIAL MATERIAL(S)**  
FAX COMPLETED FORM TO REGULATORY AFFAIRS DIVISION  
Fax: (613) 941-1708

Date Received:	Tracking #:
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**SUBMISSION INFORMATION** (Manufacturer to complete this Section, for each drug lot)

Clinical Trial Application (CTA) Control #:

Proper Name:

Trade Name:

Manufacturer:

Sponsor:

Protocol(s) #:

Date of CTA Clearance:

**DRUG PRODUCT INFORMATION**

Lot Number:

Strength/Presentation:

Date of Manufacture:

Current Expiry/Retest:

Drug Substance Batch Number(s):

Current Expiry/Retest Date:

Human-derived Excipient Product Name/Concentration:

Human-derived Excipient Manufacturer:

Human-derived Excipient Plasma Source: a) Country of Origin \_\_\_\_\_ b) Recovered  Apheresis

Human-derived Excipient Lot Number(s):

This certifies that, all release tests for the above Drug Substance and Drug Product lot(s) have been completed as outlined in the above submission; the source and testing of any associated human-derived excipients are consistent with the approved submission; and (check one box only),

- All test results are within approved specifications; or,
- Not all testing specifications have been met - testing protocol, explanation, and rationale for use are appended.

**Responsible Head, or Designate:** \_\_\_\_\_ **Phone:** \_\_\_\_\_

Fax to:	Fax No:
Signature:	Date Fax-Back Complete:

If you do not receive all pages or this transmission is not clear please contact (613) 957-1722.

Rev. 1 Rev. Date: March 18, 2005  
**Effective Date: June 1, 2005**

**APPENDIX IB**

FAX-BACK FORM  
**GROUP 4 PRODUCTS CONTAINING HUMAN-DERIVED EXCIPIENTS**  
FAX COMPLETED FORM TO REGULATORY AFFAIRS DIVISION  
Fax: (613) 941-1708

Date Received:	Tracking #:
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**DRUG PRODUCT** (Manufacturer to complete this Section, for each drug lot)

Product Name/Concentration:

Trade Name (if applicable):

Drug Identification Number (DIN):

Manufacturer:

Lot Number:

Date of Manufacture/Expiry Date:

**ASSOCIATED HUMAN-DERIVED EXCIPIENT(S)**

Product Name/Concentration:

Trade Name (if applicable):

Manufacturer:

DIN (if applicable):

Plasma Source: a) Country of Origin \_\_\_\_\_ b) Recovered  Apheresis

Lot Number:

Date of Manufacture/Date of Expiry:

This certifies that the source and testing of the human-derived excipient identified above, and associated with the drug product lot identified above, is consistent with the approved submission for the drug product and/or with subsequent agreements made with the Centre for Biologics Evaluation (CBE) or the Centre for Evaluation of Radiopharmaceuticals and Biotherapeutics (CERB)

**Responsible Head, or Designate:** \_\_\_\_\_ **Phone:** \_\_\_\_\_

Fax to:	Fax No:
Signature:	Date Fax-Back Complete:

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**APPENDIX IC**

FAX-BACK FORM  
**GROUP 4 PRODUCTS**  
FAX COMPLETED FORM TO REGULATORY AFFAIRS DIVISION  
Fax: (613) 941-1708

Date Received:	Tracking #:
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**DRUG PRODUCT** (Manufacturer to complete this Section, for each drug lot)

Product Name/Concentration:

Trade Name (if applicable):

Drug Identification Number (DIN):

Manufacturer:

Lot Number:

Date of Manufacture/Expiry Date:

**ASSOCIATED HUMAN-DERIVED EXCIPIENT(S)** Check one:  YES  NO

Product Name/Concentration:

Trade Name (if applicable):

Manufacturer:

DIN (if applicable):

Plasma Source: a) Country of Origin \_\_\_\_\_ b) Recovered  Apheresis

Lot Number:

Date of Manufacture / Date of Expiry:

This certifies that the source and testing of the human-derived excipient identified above, and associated with the drug product lot identified above, is consistent with the approved submission for the drug product and/or with subsequent agreements made with the Centre for Biologics Evaluation (CBE) or the Centre for Evaluation of Radiopharmaceuticals and Biotherapeutics (CERB)

**Responsible Head, or Designate:** \_\_\_\_\_ **Phone:** \_\_\_\_\_

Fax to:	Fax No:
Signature:	Date Fax-Back Complete:

If you do not receive all pages or this transmission is not clear please contact (613) 957-1722.

## **APPENDIX II: TARGETED TESTING**

Targeted testing specifies a combination of one or more assays, applied to all lots, for a particular biologic product. It may include a subset of tests ranging from one (1) to the complete set of assays proposed by the manufacturer in the submission of a CTA, NDS, or S/NDS. Routine lot release testing may be restricted to those critical assays in which failure to meet approved specifications may reflect product quality or safety. Certificates of Analyses are also reviewed. The targeted timeframe for products in this Group to be released is 6 weeks after receipt of all required information and samples. Certain products with lengthy bioassays may take longer.

The targeted testing regime developed for Group 2 products is based on:

- a) Risk assessment of each test as determined by i) the possibility of an incorrect test result, and ii) the risk to safety associated with an incorrect test result
- b) BGTD's experience with testing of the product and results of testing of consistency lots and/or clinical trial materials
- c) Lot failure information provided by the manufacturer
- d) Other pertinent information such as information obtained from other Regulatory Agencies, Product Recalls, and Adverse Drug Reaction reports

For products that require lengthy release tests (e.g. animal testing), concurrent testing by BGTD and the manufacturer will be considered. In the case of concurrent testing, prompt notification of any testing failures must be provided to BGTD.

### **APPENDIX III: PERIODIC TESTING**

Products in Evaluation Groups 3 and 4 are subject to Periodic Testing. Lot samples may be requested by BGTD for Periodic Testing to confirm that the product meets specifications. Lot samples are selected based on production history, inspection history, testing history and other related factors.

If lot samples have been requested by BGTD for Periodic Testing, the targeted timeframe for release is 6 weeks from the date that all required information is received.

**APPENDIX IV:**

**SUMMARY OF REQUIREMENTS FOR EVALUATION GROUPS**

<b>Evaluation Group Description</b>	<b>GROUP 1A Pre-Approval Clinical Trials</b>	<b>GROUP 1B Pre-Approval Associated with NDS or S/NDS submissions.</b>	<b>GROUP 2 Post-Approval Products requiring the highest level of assessment.</b>	<b>GROUP 3 Post-Approval Products requiring a moderate level of assessment.</b>	<b>GROUP 4 Post-Approval Products requiring a low level of assessment.</b>
<b>Sample Requirements</b>	<i>Prophylactic Vaccines:</i> Samples submitted for testing by BGTD  <i>Other Biologics:</i> No samples required	Samples from 3 to 5 consecutively manufactured lots are submitted to BGTD for lot-to-lot consistency testing	Targeted Testing (mandatory submission of samples of all lots to BGTD for testing). See Appendix II.	Products in Group 3 are subject to Periodic Testing. See Appendix III.	Products in Group 4 are subject to Periodic Testing. See Appendix III. The manufacturer must notify BGTD on an annual basis of lots sold in Canada
<b>Document Requirements</b>	<i>Prophylactic Vaccines:</i> Submission of Protocols of tests and/or CoAs to BGTD for review  <i>Other Biologics:</i> Sponsors are required to complete and file a Fax-back form, which must include a rationale if testing specifications have not been met	Submission of Protocols of tests and/or CoAs to BGTD for review	Submission of Protocols of tests and/or CoAs to BGTD for review	Submission of Protocols of tests and/or CoAs to BGTD for review	Fax-back form with lot number of product at time of sale in Canada plus information on HDE's if product contains HDE
<b>Approval Mechanism</b>	<i>Prophylactic Vaccines:</i> A written approval in the form of a release letter is required  <i>Other Biologics:</i> Fax-back form will be returned by fax to the sponsor	Upon request, lots from which consistency samples were taken may be released for sale in Canada once an NOC is issued  A written approval 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 written approval for sale in the form of a release letter is required for all lots	Not Applicable
<b>Target Timeline</b>	Not Applicable	Not Applicable	6 weeks after receipt of all required information and samples  Expedited release may be granted in exceptional cases and upon appropriate justification such as product shortage	2 weeks after receipt of all required information  If Periodic Testing samples are requested by BGTD, the target timeline is 6 weeks	If Periodic Testing samples are requested by BGTD, the target timeline is 6 weeks
<b>Reporting Requirements</b>	Not Applicable	Not Applicable	Yearly Biologic Product Report	Yearly Biologic Product Report	Yearly Biologic Product Report

**BGTD Lot Release Working Group Members**

Guidance for Sponsors: Lot Release Program  
For Schedule D (Biologic) Drugs

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