Notice: Release of the New Guidance for Industry: Management of Blood Establishment Submissions

Our Reference Number: 07-100744-884

The Biologics and Genetic Therapies Directorate (BGTD) is pleased to announce the release of the revised guidance document *Management of Blood Establishment Submissions Guidance (MBESG)*. This document is the result of a number of internal and industry consultations and has been revised as a result of both. This document will replace the version with the effective date of August 5, 2003.

The most significant changes to this document relate to the following:

a. The need to make the submission management process compliant with C.01A.014 as it relates to the 90-day default specified in this regulation.
b. The Category II Fax-back Notification has been revised. This version should be implemented immediately by blood establishments.
c. A new Fax-back for Rolling Submissions

Contacts

Questions concerning general filing requirements for Blood Establishment Submissions and the possible need for a pre-submission meeting should be directed to:

Blood Establishment Regulation Unit
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Biologics and Genetic Therapies Directorate
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Canada

GUIDANCE FOR INDUSTRY

Management of Blood Establishment Submissions

Published by authority of the
Minister of Health

Date Adopted	December 8, 2006
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Biologics and Genetic Therapies Directorate
Guidance Document

Our mission is to help the people of Canada maintain and improve their health.

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HPFB's Mandate is to take an integrated approach to the management of the risks and benefits to health related to health products and food by:

- Minimizing health risk factors to Canadians while maximizing the safety provided by the regulatory system for health products and food; and,
- Promoting conditions that enable Canadians to make healthy choices and providing information so that they can make informed decisions about their health.

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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 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 which do not have the 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 evidence and scientific justification. Alternate approaches should be discussed in advance with the Biologics and Genetic Therapies Directorate 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 the Biologics and Genetic Therapies Directorate 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. The Biologics and Genetic Therapies Directorate 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 guidance documents.

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1.0 PURPOSE

The purpose of this Guidance is to explain the way in which the Biologics and Genetic Therapies Directorate (BGTD) plans to manage submissions from blood establishments provided in accordance with the *Food and Drugs Act* and *Regulations*:

Licence Applications - C.01A.005
Licence Amendments - C.01A.006
Notices - C.01A.013 and C.01A.014

Note: Applicable regulations supersede any criteria or requirements referred to in this or other non-regulatory documents (i.e. Guidances, Canadian Standards Association standards or other standards).

2.0 BACKGROUND

The Management of Blood Establishment Submissions Guidance (MBESG) will be updated regularly to reflect changes in policies related to the blood establishment submission and review process. It is anticipated that changes to the current Guidance, as well as the introduction of additional information and clarification, will reduce the number of requests for clarification.

Industry representatives and BGTD employees may rely on the MBESG for guidance and operational direction in numerous areas including: the handling of submission information, procedures related to submission review, requests for clarification and performance targets.

3.0 SCOPE

The Guidance applies to blood establishments in respect of manufacturing of blood and blood components for transfusion, source plasma and/or recovered plasma for further manufacturing.

4.0 ABBREVIATIONS

These are the abbreviations used in the document:

BGTD	Biologics and Genetic Therapies Directorate
CPRA	Centre for Policy and Regulatory Affairs
DSTS	Drug Submission Tracking System
DSTS-IA	Drug Submission Tracking System - Industry Access
FDA	Food and Drug Administration (USA)
HC	Health Canada
MBESG	Management of Blood Establishment Submissions Guidance
NOD	Notice of Deficiency
OSE	On-site Evaluation
SIPD	Submission and Information Policy Division
MRA	Mutual Recognition Agreement

Date Adopted: December 8, 2006; Effective Date: December 8, 2006

5.0 GLOSSARY

See *Appendix A* for the Glossary of terms.

6.0 SUBMISSIONS - GENERAL

A blood establishment must file with the Minister, a submission that contains sufficient information to enable the Minister to assess the safety of the drug, in this case whole blood and its components, taking into account the proposed operations or changes to current operations. It is important that the blood establishment ensures that the information submitted is sufficient to enable the Minister to make this assessment.

The determination of whether the submission contains enough information and is of suitable quality to allow the Minister to perform the review and does not contravene any regulations will be made during this initial screening period. This is a distinct and separate process from the review of the information to assess whether the proposed change or Licence Application is acceptable or not.

If the information provided is incomplete or of inadequate quality, thereby making it impossible to proceed with the review, additional information and/or clarification may be sought from the blood establishment. Once it has been determined that the information provided is suitable for review, a letter will be issued to the blood establishment indicating that the information will be reviewed. This is the letter referred to in section C.01A.014(1)(b) henceforth referred to as the Acceptable-Screening Letter, and the date of its issue will trigger the start of the 90-day default period provided for in section C.01A.014(1)(b).

Please note that all timeframes referred to in this document are **calendar days**.

See Appendices B to E for flow charts that define the screening and review processes for blood establishment submissions.

The BGTD guidance document entitled *Blood Establishment Licence Amendment Requirements for Information Technology Submissions* will provide information on Licence Amendment requirements specific for these types of changes. Submissions made in these areas will be managed in accordance with the principles outlined in this Guidance.

6.1 Licence Application Submissions

In accordance with C.01A.004 of the *Food and Drug Regulations*, blood establishments which perform licensable activities (i.e. fabricating, packaging/labelling, testing, distributing, importing or wholesaling) in Canada must do so in accordance with an Establishment Licence.

To obtain an Establishment Licence an Establishment Licence Application must be submitted to the Health Products and Food Branch Inspectorate (HPBFI). See *http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/compli-conform/v4_nov2003_e.pdf* for guidance on HPBFI Establishment Licence Applications. A Licence Application submission must be submitted

concurrently to BGTD. See Appendix F for BGTD Licence Application submission requirements identified in C.01A.005(l).

Review of the two applications is coordinated between the two groups within Health Canada. The requirements and submission management principles outlined in this Guidance relate only to submission requirements for BGTD. All Licence Application submissions are considered to be Category IV submissions as outlined in Section 8.1 of this Guidance. However, C.01A.004 and C.01A.005 do not provide any performance targets for these types of submissions. BGTD will use performance targets and regulatory tools (See Appendix G) identified within MBESG for all Licence Application submissions.

6.2 Licence Amendment Submissions

The *Food and Drug Regulations* specify:

> *C.01A.006 (1) A person who wishes to amend an establishment licence shall submit an application to the Minister, that contains the applicable information specified in section C.01A.005.*
>
> *(2) An establishment licence must be amended where the licensee proposes*
>
> *(a) to add an activity or category of drugs, as set out in C.01A.008;*
>
> *(b) in respect of a category of drugs and activity indicated in the licence, to authorize sterile dosage forms of the category;*
>
> *(c) to add a building in Canada at which drugs are authorized to be fabricated, packaged/labelled, tested as required under Division 2 or store a category of drugs, or sterile dosage forms of the category; and*
>
> *(d) in addition to the matters set out in paragraphs (a) to (c), in the case of an importer,*
>
> *(i) to add a fabricator, packager/labeller or tester of a drug,*
>
> *(ii) to amend the name or address of a fabricator, packager/labeller or tester indicated in the licence, and*
>
> *(iii) if the address of the buildings at which drugs are authorized to be fabricated, packaged/labelled or tested is indicated in the licence, to add additional buildings or, for an existing building, to add an authorization to fabricate, package/label or test a category of drugs, or sterile dosage forms of the category.*

Licence Amendments pertaining to C.01A.006(2)(c) are those where a blood establishment intends to add or move to a new building. Generally speaking such submissions must contain information similar to that found in Appendix F although this is considered a change to current operations rather than a new Licence Application.

Addition of sub-centres or fixed sites (see Glossary, Appendix A) are submitted as Notices pertaining to C.01A.013(a) (See Section 6.3, Notices).

6.3 Notices

Sections C.01A.013 and C.01A.014 of the *Food and Drugs Regulations* provide requirements for submission of Notices to the Minister.

Changes to approved operations in respect of C.01A.013 are referred to as Category I submissions.

Changes in respect of C.01A.014 are referred to as Category II, Category III or Category IV submissions. These three submission categories have reporting requirements based on their level of risk, with Category II being the lowest risk category. See Section 8.0 and Appendix B for details.

A list of the regulatory tools applicable to each category can be found in Appendix G. See Table 1. for guidance on possible changes to blood establishment operations and the associated submission category. It must be noted that this list cannot be considered exhaustive.

In addition, BGTD reserves the right to request information or material, or define conditions not specifically described in this guidance, in order to allow the Minister to adequately assess the quality, efficacy and safety of blood and blood components and the impact of proposed changes on the donor. BGTD is committed to ensuring that such requests are justifiable and that decisions are clearly documented.

7.0 CATEGORY I SUBMISSIONS

The *Food and Drug Regulations* specify:

> *C.01A.013. Every person who holds an establishment licence shall notify the Minister in writing within 15 days after*
>
> > *(a) there is any change to the information referred to in any of paragraphs C.01A.005(a),(b),(e),(f),(h) and (i), and subparagraphs C.01A.005(g)(i) and (ii)*

In accordance with subsection C.01A.013(a) of the *Food and Drug Regulations*, blood establishments shall notify the Minister in writing within 15 days after a change to any of the following:

- The applicant's name, address, telephone number, facsimile number and electronic mail address
- The name, telephone number, facsimile number and electronic mail address of a person to contact in case of an emergency
- Whether the applicant proposes to carry out a licensed activity in respect of a drug that is a bulk process intermediate
- The address of each building in Canada in which the applicant proposes to fabricate, package/label, test as required under Division 2 or store blood and blood components, specifying for each building which of those activities will be taking place there and whether any drugs will be bulk process intermediates. Addition of sub-centres or fixed sites (see Glossary, Appendix A) are submitted as a Notice pertaining to C.01A.013(a).
- The address of each building in Canada at which records will be maintained.

7.1 Category I Submission Format

Category I submissions should be provided in letter format. The following information must be included:

- Identify as a Category I submission
- Description of change providing complete names, titles, addresses, postal codes, phone numbers, fax numbers, e-mail addresses.

See also Table 2.

8.0 CATEGORY II, III and IV SUBMISSIONS

The Food and Drug Regulations specify:

> *C.01A.014.*
> *(1) No licensee shall carry on a licensed activity in respect of any category of drugs if a change referred to in subsection (2) has occurred in respect of that category, unless*
> *(a) they have filed with the Minister a notice that contains sufficient information to enable the Minister to assess the safety of the drug, taking into account the change;*
> *(b) the Minister has issued to them a letter indicating that the information will be reviewed and has not, within 90 days after issuing the letter, sent them a notice indicating that the change is not acceptable.*
>
> *(2) Notification is required in respect of the following changes where they may affect whether a*
> *drug can be fabricated, packaged/labelled, tested or stored in accordance with the applicable requirements of Divisions 2 to 4:*
> *(a) changes to the plans and specifications of a building where a drug is fabricated, packaged/labelled, tested or stored;*
> *(b) changes to the equipment that is used in the fabrication, packaging/labelling or testing of a drug;*
> *(c) changes to the practices or procedures; and*
> *(d) in the case of an importer, other than an importer of a drug that is fabricated, packaged/labelled or tested in an MRA country at a recognized building, any change referred to in paragraphs (a) to (c) that relates to the fabricator, packager/labeller or tester of the drug being imported.*

Section C.01A.014 prohibits blood establishments from carrying on a licensed activity in respect of whole blood and its components if there has been a change in respect of the drugs that may affect whether they can be fabricated, packaged/labelled, tested or stored in accordance with the applicable requirements of Divisions 2 to 4 of the *Food and Drug Regulations*.

In order for a blood establishment to carry on a licensed activity with the change, three conditions must be met sequentially:

- A Notice must be filed with the Minister
- A letter must be issued by the Minister to the blood establishment indicating that the information is acceptable for review (i.e. **Acceptable-Screening Letter**)
- The Minister must not, within 90 days of the date of the Acceptable-Screening Letter, have issued a notice indicating that the change is not acceptable (i.e. **Unacceptable Letter** or a **90-Day Notice**).

The Minister has 90 days from the date the letter referred to in section C.01A.014(1)(b) (i.e. Acceptable-Screening Letter) is issued to the blood establishment, to perform an in-depth review of the information submitted with the Notice and assess whether the change is acceptable or not.

8.1 Determination of Submission Category

Determination of the category of a proposed change must take into account the risk that may be associated with the change itself, the risks associated with the implementation of the change and the risks of not making the change.

For the purposes of the regulatory process, risk issues may be defined as those posing potential or perceived risk to human health. The measure of both the harm to human health that may result from changes to blood establishment operations together with the likelihood that the harm will occur must be assessed by a scientific evaluation of the probability of occurrence and severity of known or potential adverse health effects resulting from the proposed change.

Submissions categorized as II, III and IV correspond to changes having minimal, moderate and substantial potential safety impact, respectively.

See Table 1. for a list of examples which should not be considered exhaustive. Clarification and advice with respect to proper category may be sought from BGTD prior to submission, in order to avoid subsequent delays or changes of category.

Table 1. Examples of Possible Changes and Associated Submission Category

Category II (minimal risk)	Category III (moderate risk)	Category IV (substantial risk)
▸ revisions to work instructions as a result of minor package insert changes ▸ revisions to work instructions for equipment maintenance and calibration	▸ use of new equipment with moderate impact (e.g. balances or centrifuges related to core processes) ▸ changes to equipment as a result of modifications to software ▸ changes in contract testing facilities ▸ new or revised work instructions for labelling	▸ new processes; new or revised work instructions requiring judgement; revisions to donor suitability, deferral or identification ▸ addition of new lab or critical equipment

Note: Editorial changes such as correction of typographical errors, case changes, added/deleted acronyms, punctuation, page numbers and updated references (e.g. change from MBESG Version 1 to MBESG Version 2) are not considered to be changes to operations and as such do not require submission to Health Canada (HC).

9.0 SUBMISSION TYPES

There are four types of submissions: Regular, Accelerated, Rolling and Extension of Approved Changes to Subsequent Sites.

9.1 Regular Submissions

All submissions are termed Regular Submissions, with the exception of Accelerated, Rolling and Extension of Approved Changes to Subsequent Sites, which are managed under certain exceptional circumstances.

9.2 Accelerated Submissions

Submissions will be assigned an accelerated status at the request of the blood establishment and as determined by BGTD, when an issue arises that results in the need to implement a change within a very short timeframe. Submissions identified as accelerated are moved to the head of the screening and/or review queue because of related safety or regulatory issues. Targeted review times will be dependent upon the circumstances and will be discussed with the blood establishment.

Examples of submissions requiring accelerated status include, but are not limited to, the following:

- An urgent situation that represents a safety concern such as a new disease that impacts the blood supply
- A short-supply issue
- Identification of a requirement for implementation of a change within a defined time frame (for example through the issuance of a Health Canada Directive or addition of a

condition to an Establishment Licence). In these cases, a prior request for accelerated status, as outlined below, is not required.

Where a blood establishment is requesting an accelerated review, it must provide a written rationale to BGTD as soon as possible, identifying the reasons why the submission should be given accelerated status and critical time lines associated with the proposed change. BGTD will review the rationale within one business day and will inform the blood establishment whether the submission will be granted accelerated status.

The blood establishment is expected to respond within an appropriate time to requests for clarification in the case of accelerated submissions.

When BGTD, through the issuance of a Health Canada Directive, requires implementation of a change to operations with a very short time frame identified, a blood establishment need not obtain BGTD agreement to identify the submission as having accelerated status. In these instances accelerated status will be associated with the submission automatically.

9.3 Rolling Submissions

On occasion, for a major change, projects requiring numerous phases (some of which occur independently of each other) or for a Licence Application, it may not be possible for a blood establishment to provide all requisite submission information in a single package. When the requisite submission information is not provided in a single package but in two or more parts, this is termed a rolling submission.

As a rule rolling submissions are not favoured or encouraged, but may be submitted when BGTD has agreed to this type of submission[1]. This applies only to Category IV submissions. It is suggested that a presubmission meeting or teleconference be requested in order to provide BGTD with details of the request for a rolling submission (See Section 12.1). Requests for rolling submissions will be assessed on a case-by-case basis. Prior approval by BGTD is required.

It is the intent of BGTD to limit the use of rolling submissions to those situations where a demonstrable need for this type of submission is identified. In order to justify a rolling submission there must be the potential for substantial risk of an adverse effect on the donor, recipient and/or product related to the proposed change, which would be reduced by a staggered approach to implementation.

At least one month prior to filing the rolling submission the following information must be provided to BGTD:

[1] Submissions provided in accordance with the BGTD guidance document *Blood Establishment Licence Amendment Requirements for Information Technology Changes* (http://www.hc-sc.gc.ca/dhp-mps/brgtherap/applic-demande/guides/qualit/blood-sang/lic_amend_oct2002_final_e.html) are already recognized as rolling submissions and prior approval for such a submission is not required.

- A rationale for the rolling submission
- A plan for provision of all required information
- A schedule detailing when all submission information is to be provided.

BGTD will issue one **Control Number** for the submission upon receipt of the first part (original information and material). Upon satisfactory completion of screening of the initial submission an **Acceptable-Screening Letter** will be issued. The first 90-day default/review target is initiated from the date of issuance of this letter.

When BGTD ascertains that there is insufficient information to determine whether a change is acceptable and the 90-day default/review period prescribed by the regulations is going to lapse, BGTD must issue a notice (i.e. **90-Day Notice**) to the submission sponsor, no later than the 90th day, indicating:

i. That the change is unacceptable for the reason that the information submitted is insufficient to determine whether or not the change is safe; that is to say that information is considered to be incomplete.
ii. The information that still needs to be addressed by the submission sponsor.
iii. That the blood establishment may not proceed to implement the changes described in the submission.

In order to be in compliance with C.01A.014 the blood establishment must then refile the submission. In order to make this process as seamless as possible a Fax-back Notification for Refiling a Rolling Submission (See Appendix H) will be issued with the 90-Day Notice. This fax-back will serve 4 purposes:

1. Identify the submission (i.e. cross-reference the original submission)
2. Provide a new Submission Certificate for the refiled submission.
3. Provide notice of acceptable screening for the refiled submission as required by C.01A.014(1)(b).
4. Identify the next 90-day review target/default.

The Control Number for the submission will remain unchanged.

BGTD will continue the review process and the sponsor must then cycle through the process again:

- Submit any additional information required to support the proposed change, identified in the 90-Day Notice.
- Await the issuance other regulatory correspondence which may include another Notice and Fax-back Notification for Refiling a Rolling Submission or, after the identified 90-day period has elapsed, implement the change.

Each new portion of the submission received will be considered as original information and material and will be assigned a **Document Number**, acknowledged and subject to screening. Where required, a **Screening Clarifax** will be issued relative to any submission of original information and material.

9.4 Extension of Approved Changes to Subsequent Sites

When a blood establishment has made a change which has been approved by BGTD and it subsequently decides to make the same change at a different site, in essentially the same way, repetitions of the same change will require Category II submissions.

Examples of Extension of Approved Changes to Subsequent Sites include, but are not limited to, the following:

- Transfer of testing from one centre to another
- Implementation of new equipment (e.g. automated testing) already approved for use at another site.

This type of Category II submission requires provision of the following:

- Description of the change to be implemented
- Rationale for extending the accepted change to a subsequent site
- Cross-reference to the BGTD Control Number of the previously accepted change
- Certification, signed by appropriate personnel, attesting that the same process and work instructions are being used to implement the change at a subsequent site and identification of any deviations from the BGTD accepted plan
- Description of training
- Details with respect to work instructions:
  - a list of the impacted work instructions and version number
  - a change rationale for any revisions to work instructions from previously BGTD accepted versions - **changes should be minor in nature**
- Proposed implementation date.

10.0 SUMMARY OF SUBMISSION REQUIREMENTS

Table 2. provides a summary of the submission categories, associated performance targets and other general information. Table 3. provides general submission requirements.

Table 2. General Submission Information

	Category I	Category II	Category III	Category IV
Legislative Authority	C.01A.013	C.01A.014	C.01A.014	C.01A.014
Potential to have an adverse effect on the safety or efficacy of the product(s) and/or on the donor or recipient	Negligible	Minor	Moderate	Substantial
Screening Performance Target (days)	N/A	20 (screening and review)	15	15
Review Performance Target (days)	N/A		30	90
Number of Copies Required	1	1	3	3

Table 3. Submission Requirements

Note: Sufficient information to evaluate the proposed change, taking into account the risk of the proposed change, must be provided. Therefore, the amount of information and the level of detail required **may** be less for a Category III submission than for a Category IV submission.

Category 1	**Category II**	**Category III**	**Category IV**
1. Identify as a Category I submission; 2. Description of change providing complete names, titles, addresses, postal codes, phone numbers, fax numbers, e-mail addresses.	Fax-back Notification – Category II Submission to be completed and provided by fax.	1. Submission Certificate; 2. Executive Summary, including but not limited to, a detailed description of proposed change and rationale for change; 3. Risk Assessment; 4. Evidence of Medical Device Bureau approval, where applicable; 5. Detailed description of changes to work instructions pertinent to the submission, including rationales for these changes. Note - it may be necessary to request the roadmap and revised work instructions; 6. Overview of training plan; 7. Overview of validation plan and summary of results; 8. Clinical and scientific data in support of the change, as applicable; 9. Impact on blood establishment software; 10. Impact on labels; any revised labels must be provided; 11. Implementation schedule.	1. Submission Certificate; 2. Comprehensive Executive Summary, including but not limited to, detailed description of proposed change and rationale for change; 3. Comprehensive Risk Assessment; 4. Evidence of Medical Device Bureau approval, where applicable; 5. New and/or revised work instructions. See Appendix J for further guidance; 6. Training Plan; 7. Validation Plan and results of validation. This must include a description of how results of validation will be provided for review - either in the current submission, or after validation is complete (but during the BGTD review process). Validation requirements can be discussed with BGTD prior to making a submission; 8. Comprehensive clinical and scientific data in support of the change, as applicable; 9. Impact on blood establishment software; 10. Impact on labels; any revised labels must be provided; 11. Implementation schedule.

11.0 POSSIBLE REVIEW OUTCOMES

The Minister has 90 days from the date the letter referred to in section C.01A.014(1)(b) (Acceptable-Screening Letter) is issued to the blood establishment, to perform a review of the information submitted with the Notice and assess whether the change is acceptable.

The possible outcomes of this review are:

a) The change is acceptable, i.e. based on the information provided, the Minister assesses the drug as safe, taking into account the change.

Two options are available to the Minister if the change is found to be acceptable:

(i) issue a notice indicating that the change is acceptable prior to expiry of the 90-day default period; or,

(ii) let the default period set out in paragraph C.01A.014(1)(b) lapse, after which time the blood establishment may go ahead with the change without any further notice from the Minister.

b) The change is not acceptable.

The Minister may conclude that a proposed change is unacceptable for one of two reasons:

(i) based on the information provided, the Minister assesses the drug as not safe, taking into account the change; or,

(ii) based on the information provided, the Minister cannot assess whether the drug is safe or unsafe, taking into account the change and thus the change cannot be deemed acceptable.

For example, in some cases, the requirement for additional information will come to light only during the course of the review. Where there is insufficient time to obtain and review additional information within the prescribed 90-day period, it will not be possible to conclude that the change is acceptable based on the information submitted to the Minister and thus, the change must be deemed unacceptable. In this case, the blood establishment must file another Notice pursuant to section C.01A.014 to complete the ensemble of information required by the Minister to assess the safety of the drug, taking into account the change. This complementary Notice (i.e. the refilled submission) would be subject to the same process as the original submission.

See Section 9.3 regarding additional outcomes for rolling submissions.

12.0 PROCEDURES

Each submission will be acknowledged in writing (**Acknowledgement Letter**). A **Control Number** will be assigned to the submission at the time it is initially received. Each installment of information submitted will be assigned a **Document Number,** including the original information and material**.** See Section 9.3 for acknowledgement of original information and material for rolling submissions and Section 12.3.1 for information on acknowledgement of Category II submissions.

All submissions and submission-related information are to be provided directly to the following:

Biologics and Genetic Therapies Directorate
Centre for Policy and Regulatory Affairs
c/o Blood, Tissues, Organs and Vaccines - Regulatory Affairs Division
Blood Establishment Regulation Unit
Locator 0701A
200 Tunney's Pasture Driveway
Ottawa, Ontario
K1A 0K9

Fax No.: (613) 948 - 3564

All submission-related correspondence must be responded to in writing or by fax directly to BGTD c/o of the address/fax identified above. If the response exceeds 15 pages or includes data in tabular format, a hard copy should be sent by courier directly to BGTD c/o Regulatory Affairs Division, Blood Establishment Regulation Unit.

12.1 Presubmission Meetings and Package Requirements

If a blood establishment is planning a major submission, a presubmission meeting is recommended.

The purpose of a presubmission meeting is to:

- Provide an opportunity for the sponsor to discuss details of the submission with HC and obtain direction regarding any areas of concern based on current experience and regulatory requirements
- Discuss the data required in the proposed submission to facilitate review
- Familiarise HC staff with the pending submission prior to its arrival
- Uncover any major unresolved problems or issues

- Provide HC with the opportunity to re-align its resources, if necessary, to accommodate evaluation of the submission.

12.1.1 Meeting Requests

Meeting requests are to be received by BGTD **in writing no less than 1 month** prior to the proposed meeting date and should include the following information:

- The purpose of the meeting
- A brief description of the issues to be discussed at the meeting
- Two or more proposed dates and times for the meeting
- Suggested attendees, other than BGTD, who may be required (e.g. Medical Device Bureau).

The blood establishment will be contacted to confirm the number of HC staff attending, the scheduled time for the meeting, and to indicate the number of presubmission meeting packages required. The package may be provided electronically to the Blood Establishment Regulation Unit for distribution within HC.

12.1.2 Presubmission Meeting Packages

Blood establishments will be requested to provide, **at least 2 weeks in advance of the meeting**, a presubmission meeting package which should include the following information:

- Agenda
- List of participants
- Purpose of the meeting
- Background information, including any presentations being made
- A list of any questions/issues to be raised by the blood establishment.

12.2 On-site Evaluations (OSEs)

During the review of a submission (most often a Category IV submission but this may also apply to Category III submissions) it may be advantageous to have a site visit to confirm any of the following:

- Review evidence or data
  - BGTD may determine that a targeted assessment of data/evidence (i.e. on-site data review), is required. This often consists of a cross-sectional document review and is performed with assistance from blood establishment specialists
- Observe processes

- View a demonstration of new equipment
- Examine records.

The blood establishments may also request that a site visit take place.

The scheduling of the OSE will be done in consultation with the blood establishment and documented in writing. One or more staff members from HC may participate in the OSE. One person from BGTD will be identified as the lead for the visit. The blood establishment will make every effort to have the appropriate subject specialists available during the site visit. All relevant documents and materials must also be available.

Results of the site visit will be verbally summarized for the blood establishment prior to completing the visit (i.e. an Exit Interview). All outcomes (i.e. actions to be taken) that are the responsibility of the blood establishment or BGTD will also be provided to the blood establishment in writing, subsequent to the site visit. Timeframes for response will be identified.

12.3 Screening of Submissions

All submission-related materials will be screened by BGTD for acceptability, including but not limited to, acceptable quality and completeness for the purpose intended. Screening will also determine if the proposed change is in compliance with the regulations. This is a process distinct from, and prior to being accepted for, quality and/or clinical review.

In the responses to Screening Clarifaxes, sponsors should clearly identify in a covering letter the Control Number of the relevant submission, the purpose of the correspondence and must include a copy of the correspondence provided by BGTD (e.g. the Screening Clarifax).

12.3.1 Category II Submissions - Screening/Review

Category II submissions fall under C.01A.014 which dictates a 90-day default period for review. However, BGTD has established a **20-day combined screening/review performance target,** during which the submission will be evaluated to determine the safety/appropriateness of the proposed change.

To comply with the requirements of C.01A.014(b), BGTD must acknowledge receipt of the Category II Fax-back Notification (See Appendix I) in order to begin the 90-day default review period. There are three possibilities for this determination, outlined in Table 4.

Table 4. Category II Determination of 90-Day Default

Outcome	90-Day Default Trigger
1. Acceptable after screening/review	Date the Fax-back Notification is received in BGTD.
2. Change of Category	The 90-day review default will begin with the date of issue of the Change of Category letter. A screening period will be identified on the Fax-back Notification 15 days from the date of receipt in BGTD.
3. Change of Category (Refiling Required)	Date the Fax-back Notification is received in BGTD. The Category II submission is identified as unacceptable.

If clarification is required for a Category II, it will be done by teleconference only, no **Screening or Review Clarifaxes** will be issued. BGTD will document the results of the teleconference and provide confirmation of any clarifications, to the blood establishment, through the Fax-back Notification.

If original information and material is found to be acceptable on screening/review, the Fax-back Notification form indicating that the change is acceptable will be signed by BGTD and faxed back to the submission sponsor.

If deficiencies, regulatory and/or scientific, are identified during the screening/review of original information and material submitted as a Category II submission, BGTD will complete the Fax-back Notification indicating that the change is not acceptable and therefore may not be implemented. An explanation for the BGTD decision will accompany the Fax-back Notification.

If BGTD has determined that the change should have been submitted in another submission category the sponsor will be notified of the new submission category with the Fax-back Notification. There are two possible Change of Category Letters:

- **Change of Category**

  The information and material provided is acceptable for review. Any screening issues identified will accompany the Change of Category Letter. It may be necessary to subsequently use other regulatory tools (See Appendix G). The Control Number assigned to the submission will remain the same.

- **Change of Category (Refiling Required)**

  The sponsor will need to make a new submission in the appropriate category. Requirements for refiling will be identified in the Change of Category Letter. The

original submission will be deemed unacceptable. A new Control Number will be assigned to the new submission - sponsor must cross-reference the original submission.

In certain circumstances it may be necessary to apply conditions to the approval of a Category II Licence Amendment, however, these situations should not occur frequently.

12.3.2 Category III and Category IV Submissions - Screening

All information and material forming elements of a submission will be screened for suitability as outlined in Section 12.3.

BGTD will target **a screening period of 15 calendar days** from receipt, for all Category III and IV submission-related information.

Possible actions taken as a result of screening are:

1. Clarification and/or quality issues identified; Screening Clarifax issued.
2. Deficiencies that preclude continuing the review identified; Screening-Deficiency Notice issued.
3. Acceptable for review; Acceptable-Screening Letter issued.
4. Submission is identified as being in the wrong submission category. In this case there are 2 options:
    a. Change of Category
    b. Change of Category (Refiling Required).
5. The proposed change is unacceptable due to non-compliance with a regulation; Unacceptable Letter issued.

These documents are discussed in detail in the following sections.

12.3.2.1 Screening Clarifax

The purpose of a **Screening Clarifax**, is to ensure that the original information and material contains the requisite information for the type of submission, is of suitable quality for review and is in compliance with all pertinent regulations. BGTD uses this mechanism of addressing elements requiring clarification in Category III and IV submissions as frequently as possible.

The sponsor will be advised that solicited information identified in the Screening Clarifax must be submitted within 15 days of the date of the request or as identified. A response is considered complete if all clarifications or questions identified are addressed. Should a sponsor feel that it is not necessary to develop or file requested information, a sound rationale for this position must be presented in order for the response to be considered complete.

There is no limit to the number of Screening Clarifaxes that may be issued for submissions in Categories III and IV. However, no particular issue will be addressed more than once in a Screening Clarifax.

12.3.2.2 Screening-Deficiency

If deficiencies are found during screening of original information and material that preclude the continuation of the review, they will be identified in a **Screening-Deficiency Notice** sent to the sponsor. The blood establishment will be required to submit all of the requested information and material identified in the Screening-Deficiency Notice, within 35 calendar days from the date of request, or as agreed upon with BGTD.

After receipt of the information requested in a Screening-Deficiency Notice, a new screening period commences (with a new performance target). If, following screening, the information is found to be acceptable for review, an **Acceptable-Screening Letter** will be issued identifying the date the submission becomes part of the review workload, that is, the date which initiates the 90-day default period mandated by C.01A.014. If the response is found to be deficient, an **Unacceptable Letter** will be issued.

If the sponsor fails to provide all requested information within 35 calendar days or the submitted information is incomplete or contains unsolicited information, the original information and material will be rejected and returned to the sponsor. An **Unacceptable Letter** will be issued by BGTD. If the sponsor wishes to resubmit the information and material at a future time (i.e. refile the submission), it will be processed as new information and material and will be assigned a new Control Number.

12.3.2.3 Acceptable for Review

If, following screening, submission-related information is found to be acceptable for review, an **Acceptable-Screening Letter** will be issued confirming the date the submission becomes part of the review workload, that is, the date which initiates the 90-day default period mandated by C.01A.014.

12.3.2.4 Change of Category

If BGTD has determined that the change should have been submitted in another submission category the sponsor will be notified. There are two possible Change of Category Letters:

- **Change of Category**
  The information and material provided is acceptable for review. Any screening issues identified will accompany the Change of Category Letter. It may be necessary to

subsequently use other regulatory tools (See Appendix G). The Control Number assigned to the submission will remain the same.

- **Change of Category (Refiling Required)**
The sponsor will need to make a new submission in the appropriate category. Requirements for refiling will be identified in the Change of Category Letter. The original submission will be deemed unacceptable. A new Control Number will be assigned to the new submission - sponsor must cross-reference the original submission.

12.3.2.5 Unacceptable Following Screening

If, following completion of the screening process for a Category III or IV submission, it is found to be unsatisfactory/inadequate or does not fully comply with the requirements of the *Food and Drug Act* and *Regulations*, an **Unacceptable Letter** will be issued.

The issues identified in all parts of the screening review will be specified. Only one Unacceptable Letter per submission will be issued. Review of the submission will stop on the date the Unacceptable Letter is issued.

If the sponsor wishes to refile the appropriate information and material it will be considered a new submission.

12.4 Review of Submissions

Following issue of either an Acceptable-Screening Letter or a Change of Category Letter, Category III and IV submissions will undergo scientific and/or clinical review. Issuance of either of these letters will trigger the 90-day default review period referred to in C.01A.014.

12.4.1 Possible Actions Resulting from Review - Category III and IV Submissions

Possible actions taken as a result of review are:

1. Issues requiring clarification are identified; Review Clarifax issued.
2. Deficiencies that preclude continuing the review identified; Notice of Deficiency issued.
3. Submission is identified as being in the wrong submission category; in this case there are 2 options:
    a. Review Change of Category
    b. Review Change of Category (Refiling Required).
4. The proposed change is unacceptable; Unacceptable Letter issued.
5. The proposed change is acceptable; Acceptable Letter issued.

6. The proposed change is acceptable, however, the review has identified conditions to be attached to the decision; **Acceptable with Conditions Letter** issued.
7. A blood establishment requires BGTD acceptance in order to proceed with partial implementation of a licensable activity prior to the completion of the review; **Permission to Proceed Letter** issued.

These documents/outcomes are discussed in detail in the following sections.

12.4.1.1 Review Clarifax - Category III and Category IV Submissions

The purpose of a Review Clarifax is to expand on, add precision to or re-analyse existing information or data wherever required for the scientific/clinical review. BGTD uses this mechanism of addressing elements requiring clarification in submissions as frequently as possible.

The sponsor will be advised that the solicited information must be submitted within 15 days from the date of the request or as identified. A response is considered complete if all clarifications or questions identified in the Clarifax are addressed. Should a sponsor feel that it is not necessary to develop or file requested information, a sound rationale for this position must be presented in order for the response to be considered complete.

There is no limit to the number of Review Clarifaxes that may be issued for one submission. However, no particular issue will be addressed more than once in a Review Clarifax. If a request for clarification is identified in a Clarifax and the response is not satisfactory a **Notice of Deficiency** (NOD) or an **Unacceptable Letter** (see 12.4.1.2 and 12.4.1.4 respectively for details) will be issued.

12.4.1.2 Notice of Deficiency (NOD)

If deficiencies and/or significant omissions that would preclude continuing the review are identified during the review of a Category III or IV submission, an NOD will be issued. The difference between an Unacceptable Letter and an NOD is that the review of the submission is not complete when an NOD is issued. The review is considered complete if an Unacceptable Letter is issued. However, in order to be compliant with C.01A.014, review of the submission will stop on the date the NOD is issued and the sponsor must refile the submission in order to proceed with the proposed change.

All deficiencies identified will be specified. However, as the review cannot be considered complete there may be issues as yet unidentified.

12.4.1.3 Change of Category

During the scientific/clinical review of a submission it may become evident that the submission has been made in an incorrect category. A letter will be issued as follows:

- **Change of Category**
  The information and material provided is acceptable for review, and no further information is required at that time. It may be necessary to subsequently issue a Review Clarifax or use other regulatory tools (See Appendix G). The Control Number assigned the submission will remain the same, however, the performance targets will be modified.

- **Change of Category (Refiling Required**)
  The sponsor will need to make a new submission in the appropriate category. Requirements for resubmission will be identified in the Change of Category Letter. The original submission will be deemed unacceptable. A new Control Number will be assigned to the new submission. The sponsor must cross-reference the original submission.

12.4.1.4 Unacceptable

After the comprehensive review of a Category III or IV submission is complete, an Unacceptable Letter will be issued if the submission is found to be unsatisfactory and/or does not comply with the requirements of the *Food and Drugs Act* and *Regulations*.

The issues identified in all parts of the review will be specified. Only one Unacceptable Letter per submission will be issued. Review of the submission will stop on the date the Unacceptable Letter is issued.

If the sponsor wishes to refile the appropriate information and material it will be considered a new submission.

12.4.1.5 Acceptable

Once the review of a Category III or IV submission is complete and the proposed change is found to be acceptable, BGTD will issue an Acceptable Letter which allows a blood establishment to proceed with implementation.

12.4.1.6 Acceptable With Conditions

An **Acceptable With Conditions Letter** may be issued with conditions at the completion of a review, if required. Conditions may relate to a number of issues, including but not limited to the following:

- Reports required on implementation of the accepted change
- Reports on studies to be completed by the blood establishment post-implementation.

Responses related to the conditions specified will be termed **Post-Clearance Data** and will be reviewed. If necessary, requests for clarification or further regulatory actions may be taken as a result of the review of Post-Clearance Data.

Once review of these data is complete and all items identified in the Acceptable with Conditions Letter are considered resolved, the submission will be closed with the issuance of a **Submission-Closed Letter.**

12.4.1.7 Permission to Proceed

Subsequent to the review of a specific part of a Category IV submission, BGTD may issue a Permission to Proceed Letter in order to allow a blood establishment to proceed with the implementation of a part of the submission prior to receiving final acceptance.

12.5 Withdrawal of Submission by Sponsor

At any time during the screening or review of a submission, it may be withdrawn by the sponsor. Notification must be made in writing. BGTD will consider the submission withdrawn without prejudice to refiling.

12.6 Division of a Submission

During the screening or review of a submission, BGTD may decide that the review could be completed more efficiently by dividing the original submission into two or more separate submissions. The submission sponsor may also request that a submission be divided.

Blood establishments will be notified of the division of a submission in the **Acceptable-Screening Letter** issued for the original submission or, if the decision is made during the review period, the sponsor will be notified in writing. A separate control number will be assigned to each section of the original submission. Different categories may be assigned to separate parts of a divided submission.

13.0 REQUEST FOR RECONSIDERATION

Sponsors may file a Request for Reconsideration[2] following the issuance of one of the following final decisions:

- Unacceptable Licence Applications, Licence Amendments and Notices
- NOD
- Change of Category (Refiling Required)

14.0 REFILED SUBMISSIONS

A refiled submission is one that a sponsor files after any of the following actions or outcomes:

- Withdrawal of a submission by a sponsor
- Subsequent to the issuance of any of the following letters:
  - Unacceptable Letter
    - includes Unacceptable Licence Applications, Licence Amendments and Notices
  - NOD
  - Change of Category (Refiling Required)

In all cases, a refiled submission is considered to be a new submission and will be assigned a new Control Number and managed according to the MBESG. A refiled submission is subject to any applicable BGTD policies, procedures or guidelines that may be in effect at the time of refiling and sponsors are required to update their submissions accordingly. The applicable performance targets for the submission category apply. The refilled submission must cross-reference the original submission.

See Section 9.3 for the refiling of rolling submissions.

14.1 Refiling Within 2 Years

If a submission is refiled within 2 years the sponsor may resubmit only information and material pertaining to the deficiencies identified in the relevant letter.

For all refilings, sponsors are required to provide a summary of the differences between the original and refiled submissions including a rationale for a re-evaluation of the submission by

[2] For further information on Request for Reconsideration refer to the *Health Canada Guidance: Reconsideration of Final Decision Issued for Human Drug Submissions*, November 2005 (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/revision-final/decisions_hum_drug_drogue_e.html).

BGTD. They must also certify that the remaining information and material previously submitted remains unchanged. The refiled submission must cross-reference the original submission.

14.2 Refiling After 2 Years

If a submission is refiled more than two years after the issuance of any correspondence identified in Section 14.0, the sponsor is required to resubmit all information and material for the submission. Cross-referencing is not acceptable in lieu of resubmitting the information. In order to increase the efficiency of the review process, information and material which was previously submitted in the original submission and remains unchanged should be clearly identified and certified as such by the sponsor.

14.3 Refiling After the Sponsor Withdraws a Submission

If a submission is refiled following withdrawal by the sponsor, the sponsor is required to resubmit all information and material for the submission. Cross-referencing is not acceptable in lieu of resubmitting the information.

15.0 ACCESSING SUBMISSION INFORMATION

15.1 Reviewer Reports

Sponsors will receive reviewer reports from BGTD following receipt of an NOD, an Unacceptable Licence Application Letter or an Unacceptable Letter.

15.2 Drug Submission Tracking System - Industry Access

Sponsors may access information about their own submissions through the Drug Submission Tracking System - Industry Access (DSTS-IA). The application is web-based, with 128-bit encryption, support for SSLv3 and cookie controls. Access will be granted via user names and passwords. Information available via the DSTS-IA includes:

- Tombstone submission information
- Submission status (includes status and dates)
- Blood & plasma product information (includes manufacturer)
- Documents issued and received, including dates
- Review streams including stream, Division, status of the review and dates.

For information on obtaining accounts, sponsors may contact the Submission and Information Policy Division at *SIPD-ClientInformation@hc-sc.gc.ca*.

15.3 Status Requests

In an effort to streamline administrative processes and expedite submission review, BGTD will respond to requests concerning a submission's progress through contact with the Blood Establishment Regulation Unit, Centre for Policy and Regulatory Affairs. Such requests should be limited, to prevent reviewer's time from being eroded by repeated inquiries.

Information will be provided to sponsors in keeping with the confidential nature of the process and without prejudice to the final decision of BGTD on the disposition of the submission.

Appendix A
Glossary

Some of the terms used in this Guidance are described or defined in order to ensure uniform interpretation of the text by all.

Accelerated Submission

Accelerated submissions are those that are moved to the head of the screening and/or review queue for review without delay because of safety or regulatory issues.

Acceptable Letter

Letter issued to the blood establishment informing it that review of the submission is complete and has been found acceptable for implementation.

Acceptable Licence Application Letter

Letter issued to the blood establishment informing it that review of its Licence Application is complete and the information has been found acceptable for implementation.

Acceptable-Screening Letter

Letter issued to the blood establishment informing it that the screening of original information and material is complete and the submission has been found satisfactory for review.

Acceptable with Conditions Letter

Letter issued to the blood establishment informing it that review of the original information and material is complete and the submission has been found acceptable for implementation; however, certain conditions are imposed and must be respected by the blood establishment.

Acknowledgement Letter

Notification provided to the sponsor indicating the date the submission was received, the type of submission, the Control Number and Document Number assigned to the portion of the submission received.

Blood Establishment

Any facility licensed, or filing a licence application, in Canada to perform any of the following activities in relation to blood or blood components: fabrication, packaging/labelling, testing, distribution, importation or wholesaling.

Change of Category Letter

If a change requested by the blood establishment is found to belong in a different submission category by BGTD, a Change of Category Letter will be issued to indicate to the blood establishment the correct category for that change.

Control Number

A Control Number is a unique tracking number (6 digits) that is assigned by BGTD to each submission. This number is to be referenced in all correspondence pertaining to the submission.

90-Day Notice

The letter referred to in C.01A.014(1)(b), issued by BGTD before expiry of the 90-day review period provided for in the *Food and Drug Regulations*, indicating that the change is not acceptable.

Document Number

A Document Number is the number assigned by BGTD to each document/package of information submitted.

Extension of Approved Changes to Subsequent Sites

A process that allows a blood establishment to submit a major change as a Category II submission, when essentially the same change has been previously approved by BGTD, for the same sponsor.

Fax-back Notification – Category II Submissions

A form used for Category II submissions that is completed by the sponsor and signed by BGTD indicating the outcome of the screening/review.

Fax-back Notification for Refiling a Rolling Submission

A form used for refiling a Rolling Submission once a 90 day default timeframe has been reached.

Fixed Site

A permanent collection site providing a secure environment, where equipment and/or supplies may remain, in between the times that clinics are held.

Licence Amendment Submission

A submission to make certain changes, identified in C.01A.006, to licensed operations.

Licence Application Submission

A submission required to obtain an Establishment Licence to perform any of the following activities relative to blood and blood components in Canada: fabricating, packaging/labelling, testing, distributing, importing or wholesaling, in accordance with C.01A.004.

Mobile Site

A blood collection site where all equipment necessary for collections is taken to the site by blood centre staff and removed once the clinic is complete.

Notice

A submission to make certain changes to approved operations in respect of C.01A.013(a) and C.01A.014(2), to licensed operations (i.e. fabrication, packaging/labelling, testing, distribution, importation or wholesaling).

Notice of Deficiency

Letter issued to blood establishments informing them of deficiencies and/or significant omissions that would preclude continuing the review. All deficiencies identified in those parts of the submission that have been reviewed to date will be specified.

Original Information and Material

Information and material (e.g. blood bags, photos, comparator charts etc.) initially provided for review as part of a submission. Information provided through Clarifax requests is considered to be solicited, rather than original.

Performance Target

A deadline that is not indicated in a regulation.

Permission to Proceed Letter

Letter issued to blood establishments subsequent to the review of a specific part of a submission in order to allow the blood establishment to proceed with limited implementation of the proposed change, prior to receiving final acceptance.

Post-clearance Data

Data that must be provided on a case-by-case basis to BGTD subsequent to the conditional approval of a submission.

Presubmission Meeting

A meeting between Health Canada and a blood establishment when a major submission is planned.

Presubmission Package

Information package to be submitted by a blood establishment two weeks in advance of a presubmission meeting.

Review Clarifax

A Clarifax, issued during the scientific/clinical review of a submission to expand on, add precision to or re-analyse existing information or data in the submission.

Roadmap SOP

The operating procedure upon which the revised operating procedure has been built.

Rolling Submission

When the requisite submission information, for a major submission, is not provided in a single package but in two or more discrete parts.

Screening

A type of review used to ensure that the information and material submitted by the sponsor is complete, of suitable quality for further review and ensures compliance with regulations.

Screening Clarifax

A Clarifax issued during the screening process to clarify/ensure that the submitted information and material contains the requisite information for the type of submission and addresses any quality and/or regulatory issues identified.

Screening-Deficiency Notice

Notice issued to the sponsor when deficiencies are identified during screening of original information and material. All deficiencies identified in those parts of the submission that have been reviewed to date will be specified.

Sponsor

The blood establishment making a submission.

Sub-centre

A fixed site where some elements of component production take place.

Submission-Closed Letter

Once all items identified in an Acceptable with Conditions Letter are considered resolved, the submission will be closed with the issuance of a Submission-Closed letter.

Unacceptable Letter

Letter issued to a blood establishment when the screening or review of a submission is complete and the submission remains unacceptable from a regulatory and/or scientific perspective. All outstanding deficiencies/issues will be identified.

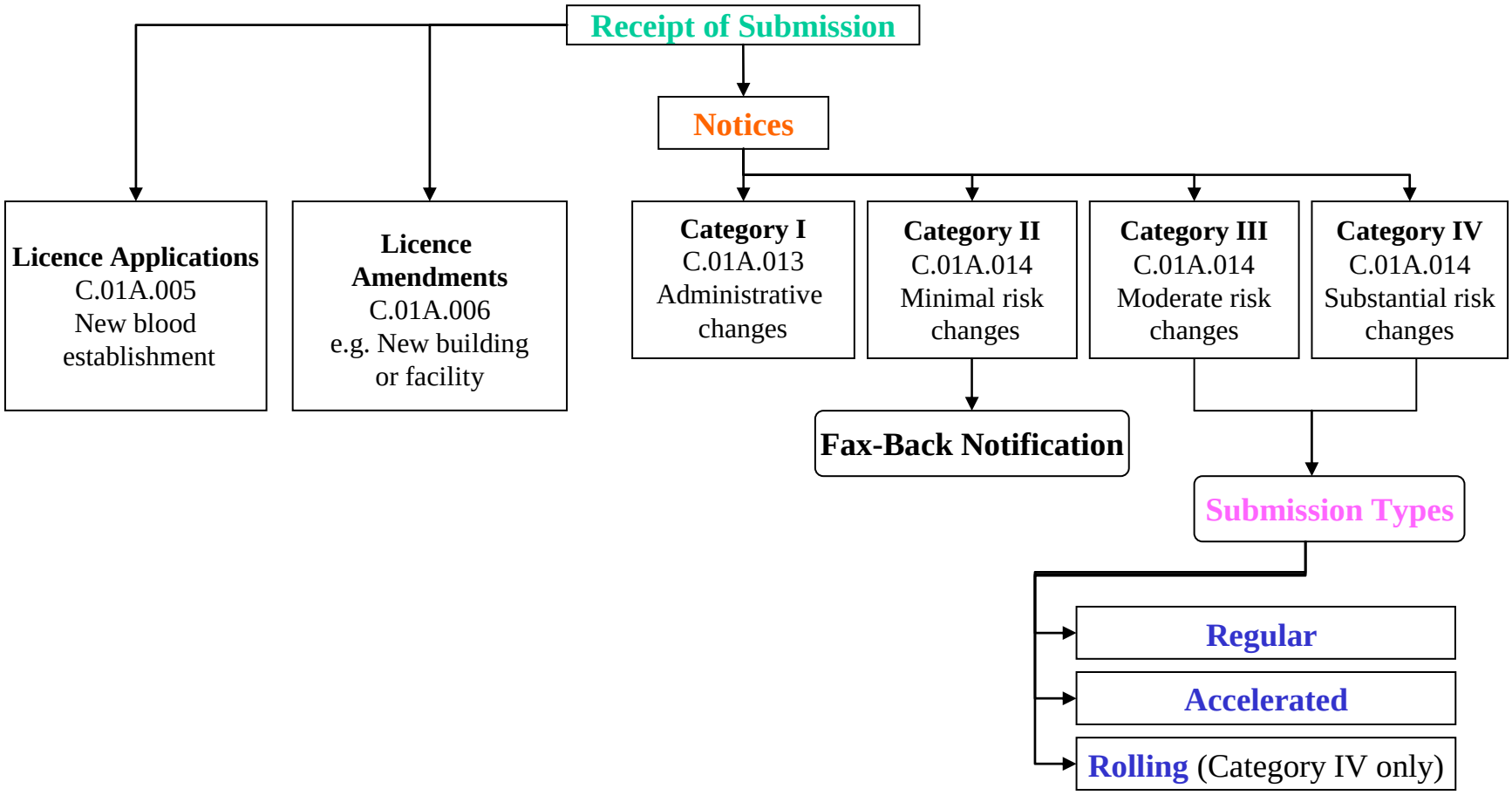
Unacceptable Licence Application Letter

Letter issued to a blood establishment when the review of a Licence Application submission is complete and the submission remains unacceptable from a regulatory and/or scientific perspective. All outstanding deficiencies/issues will be identified.

Work Instructions

Any work instructions provided to blood establishment staff to enable them to adequately perform their duties. **May** include Standard Operating Procedures (SOPs), job aids, Directives, Memos etc.

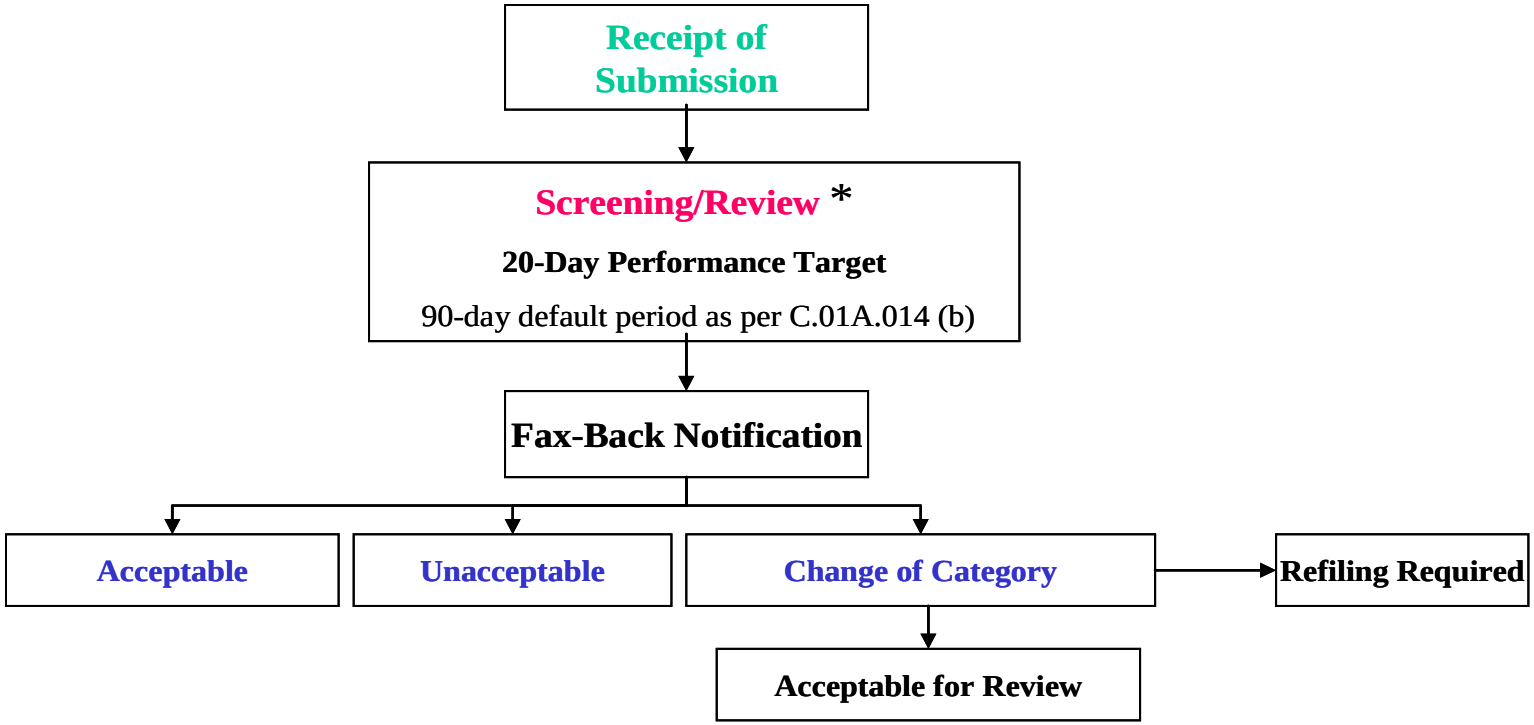
Appendix B
Submissions - General



Appendix C

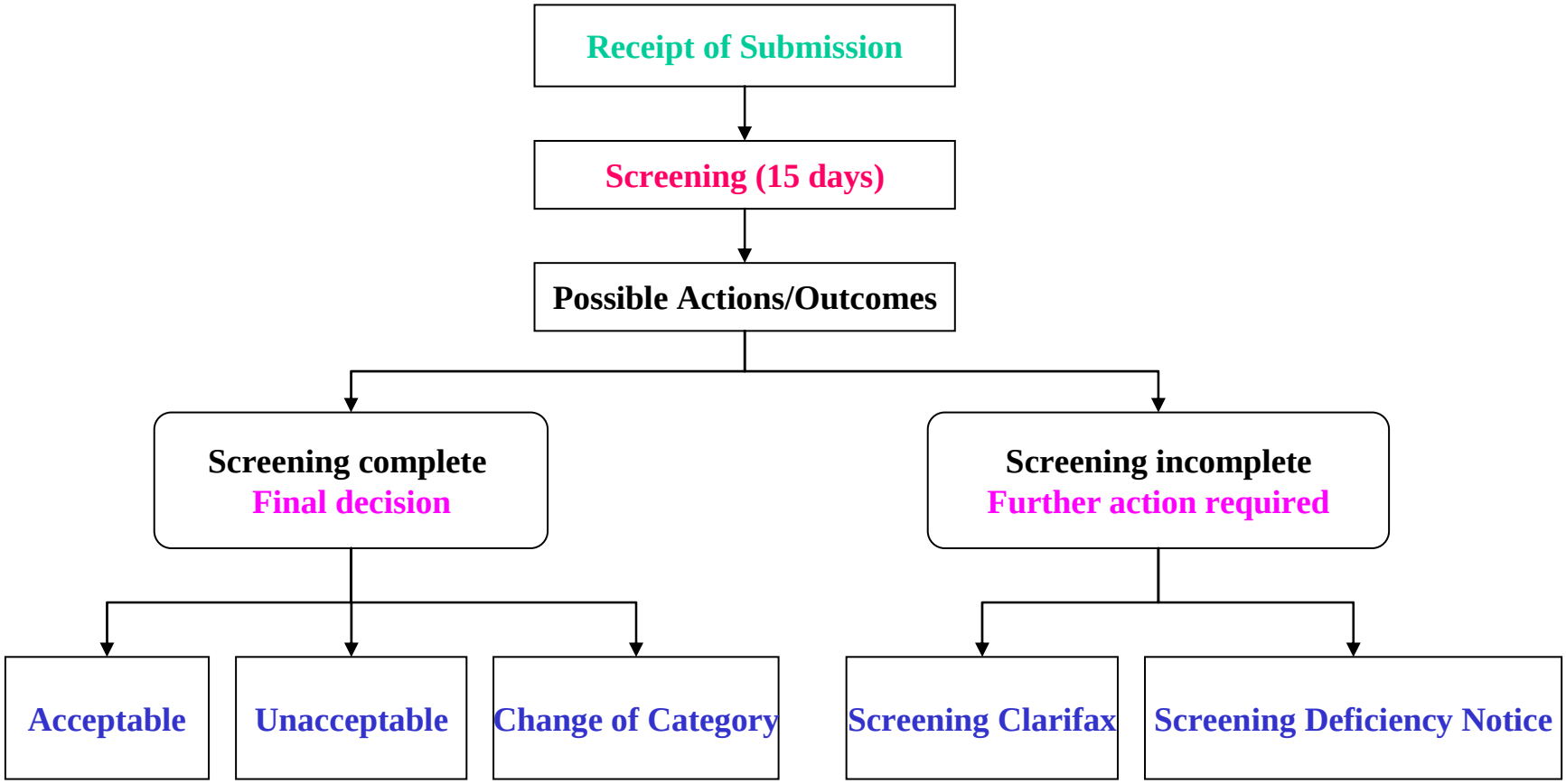
Screening/Review Process

Category II Submissions

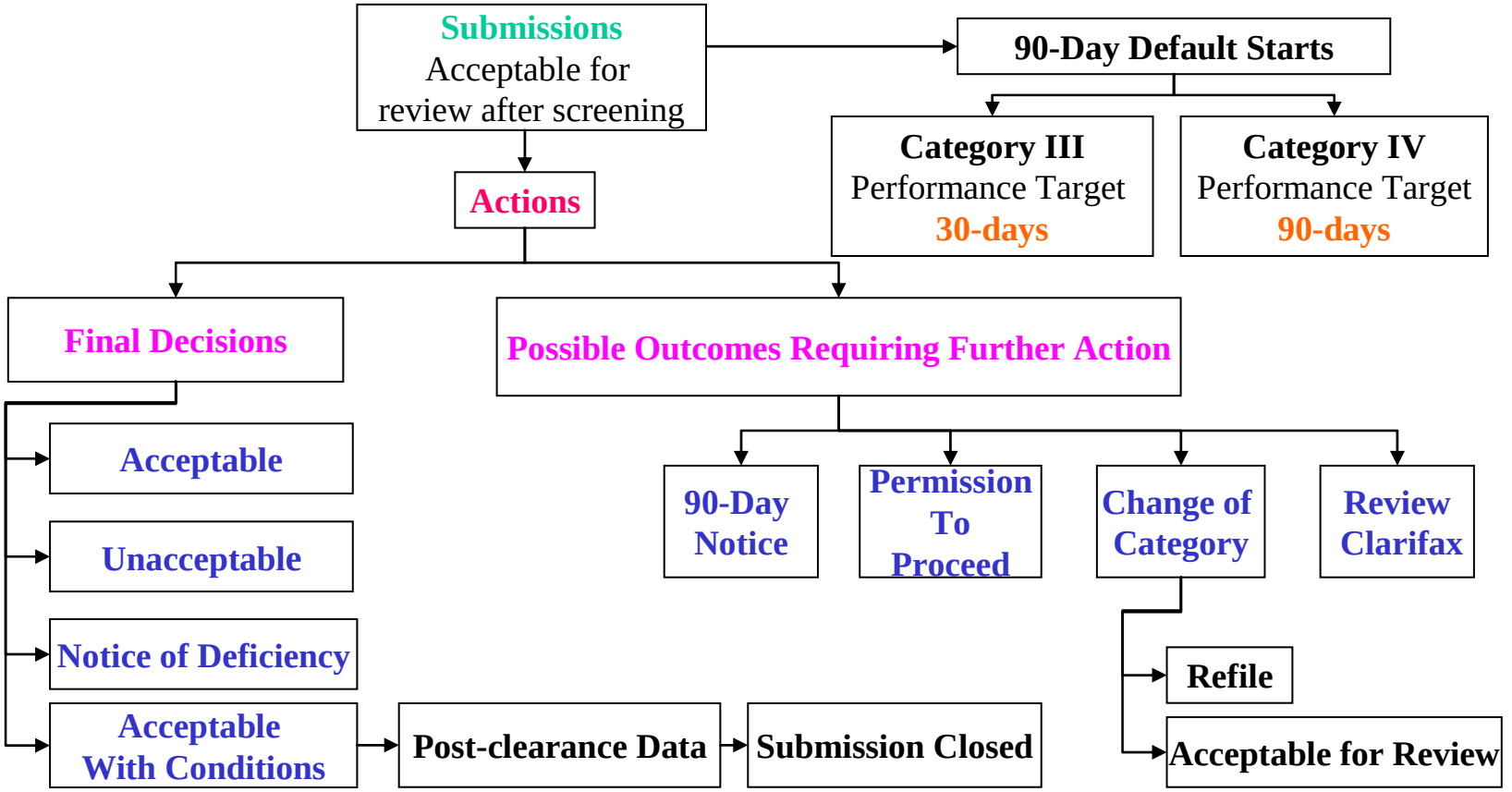


* If clarification is required it will be addressed by telephone and documented with the Fax-Back Notification

Appendix D
Screening Category III and IV



Appendix E
Review, Category III and IV



Appendix F

Licence Application Information Requirements

1. Blood Establishment Operations

- A clear and detailed description of all operations to be performed at the facility
- A clear description of all blood and blood components to be fabricated at the facility
- A clear description of a policy regarding unused units/components

2. Facilities and Equipment

A detailed description of the facilities and equipment employed in the operations, with particular attention to the following areas:

- Facilities and equipment must be appropriate and adequate for the type of intended operation (s)
- The provision of adequate storage space and conditions
- Adequate and sufficient space and equipment to allow the segregation of tested, untested and reactive units
- Adequate and properly documented installation procedures and a regular preventive maintenance schedule for the equipment
- Quality Control (QC) and Quality Assurance (QA) procedures respecting equipment (e.g. calibration procedures, QC tests included in test runs etc.).

3. Reagents, Kits and Other Items

- List and provide a description of all major supplies related to centre operations (e.g. blood shakers, Hb/Hct measuring instruments, blood pressure/temperature measuring devices, blood bags, blood collection supplies, blood screening test kits, reagents etc.)
- QC schedule and results for all major supplies.

4. Labelling

- List and provide sample labels (base, overlabels and tags) to be used
- Evidence of appropriate validation of labels and labelling methods to be used for the applicable time of storage
- Provide information concerning ISBT 128 international labelling standards - do the proposed labels comply with ISBT 128. If not, explain if it is the intention of the blood establishment to comply with ISBT 128 in future? If so, when?

5. Personnel, Supervision, Responsibilities and Administration

- Provide a current approved organization chart

- Describe organization positions and titles and clearly defined responsibilities (i.e. job description) for medical/technical supervision including the medical director and administration staff
- Provide evidence of properly qualified staff to be employed in collection/manufacturing operations
- An overview of initial and ongoing training for staff employed directly in collection/manufacturing operations
- Evidence of independence of QA functions.

6. Operations

- Provide a complete sets of work instructions for all collection/manufacturing activities.
- Provide details on record systems and record-keeping forms and procedures employed to ensure the traceability of each unit collected as well as providing for the ease of future problem investigation.
- Describe the error/incident reporting system for all areas of operations.
- Provide details on how the sponsor will assure continuity of operation.
- Provide details on how all legal responsibilities/liabilities will be met.

7. Donor and Product Safety and Security

- Provide details on donor suitability criteria.
- Provide a prototype of a consent form to be signed by donors.
- Describe procedures to be used to report and manage donor reactions.

8. Adequate Testing

A. Testing performed by establishment licence holder for their own products:

- Provide details of transmissible disease and serology testing (may vary with type of operation and policies) to be employed in blood screening testing
- Provide algorithms to be used for each marker, in case of initial reactive tests.

B. Testing performed by a contract testing facility in Canada:

- Provide details of transmissible disease and serology testing (may vary with type of operation and policies) to be employed in blood screening testing
- Provide algorithms to be used for each marker, in case of initial reactive tests
- Provide evidence that the facility has an Establishment Licence for testing blood as part of the donor screening process
- Provide evidence of agreement(s) with lab(s) to be used with complete description of labs, personnel, testing methods, reagents, validation and QA
- A method for ensuring timely receipt of all test results must also be provided.
- Proof of a system of audit for internal and/or external contracted testing facilities.

C. Testing performed by a foreign testing facility:

- Provide details of transmissible disease and serology testing (may vary with type of operation and policies) to be employed in blood screening testing
- Provide algorithms to be used for each marker, in case of initial reactive tests
- A list of all kits, including the version number currently in use at the facility
- Version number or date of the Package Insert in use
- Certification that the kit is FDA approved or alternatively, approval to use the kit must be obtain from BGTD
- Evidence of the regulatory status of the testing facility (e.g. FDA licence, AABB Accreditation, CLIA licence etc.
- Confirmation of the date of the last audit by the blood establishment of the contract facility and the proposed timeframe for following audits
- A copy of the most recent FDA 483, where applicable, and a copy of the response provided
- Proof of a system of audit for internal and/or external contracted testing facilities.

9. Unit Release and Responsibilities

- Provide a clear description of procedures to be used to release units including responsibility for the final release (e.g. QA)
- Provide a description of procedures to be employed if units are released in error.

10. Transport Chain

- Describe the validated methods to be employed for transport of released units, under proper conditions
- Describe the validated methods to be employed for transport of sample specimens to contract labs or to different geographical locations of a blood establishment.

11. Quality Assurance Program

- Detail all ongoing verification and validation procedures to be performed to ensure that all blood collection centre operations are in order and conform to approved standards and procedures
- Provide details for QA of all relevant steps
- Provide details for QC of all relevant steps.

12. Information Systems

- Details of the functions performed must be provided for any computerized systems used which perform one or more of the following functions:
    - Data handling between automated devices
    - Maintenance of data that are used in making decisions regarding the suitability of blood or blood components for transfusion or further manufacture

- Maintenance of data used to trace a unit of blood or a blood component from the source to its final disposition.

13. Error/Accident, Adverse Transfusion Reaction and Post Donation Information Reporting

- Describe procedures and responsibilities for collating, analysing and applying corrective actions regarding all Error/Accident and Adverse Reaction data
- Describe procedures and responsibilities for receiving and managing Post-Donation Information.

14. Serious Donor Events

- Describe procedures and responsibilities for receiving and managing reports of Serious Donor Events.

15. Lookback/Traceback Reporting

- Describe procedures to be used for lookback/traceback.

16. Training

- A training plan must be provided that includes, but is not limited to, details on the following:
  - who will be providing training, indicating the credentials of the trainer (e.g. train the trainer program, equipment manufacturer representative etc.)
  - how will the training of staff be documented
  - how will the training program be delivered (e.g. sign and read, web based training, hands-on etc.)
  - description of the re-certification program for employees
  - timing of training.

17. Other

- Any other information pertinent to the safety of the blood components produced.

Note: If the requirements within a given section are contained within a specific SOP or work instruction then please provide a cross reference to the SOP or work instruction in which the information can be found.

Appendix G
Regulatory Tools

Submission-Related Correspondence	**Issued when .....**
Acceptable Letter - includes Licence Applications, Licence Amendments and Notices	- a submission has been reviewed and found acceptable for implementation
Acceptable-Screening Letter	- a submission has been screened and found acceptable for review
Acceptable with Conditions	- a submission has been reviewed from a scientific and/or clinical perspective and has been found acceptable but it has been necessary to request data collected after implementation
Acknowledgement	- a submission has been received at BGTD - identifies the relevant submission tracking numbers (i.e. Control Number and Document Number), date received etc.
Change of Category	- screening and/or review of a submission determines that it has been provided in an incorrect category - the information and material provided is acceptable for review and no further information is required to continue the submission process - the Control Number remains unchanged
Change of Category (Refiling Required)	- screening and/or review of a submission determines that it has been provided in an incorrect category - the sponsor will need to make a new submission in the appropriate category - submission requirements for refiling will be identified in the Change of Category Letter - the original submission will be deemed unacceptable - a new Control Number will be assigned to the new submission - sponsor must cross-reference the original submission

Submission-Related Correspondence	**Issued when .....**
90-Day Notice	- BGTD ascertains that there is insufficient information to determine whether a change is acceptable and the 90-day default period prescribed by the regulations is going to lapse - the notice must indicate: i. That the change is unacceptable for the reason that the information submitted is insufficient to determine whether or not the change is safe: that is to say that information is considered to be incomplete. ii. The information that still needs to be addressed by the submission sponsor. iii. That the blood establishment may not proceed to implement the proposed change described in the submission.
Notice of Deficiency	- the review of a Category III or IV submission has identified deficiencies that preclude the continuation of the review - sponsor must refile the submission addressing the deficiencies.
Permission to Proceed	-review of a specific part of a submission allows the blood establishment to proceed with limited implementation of the proposed change, prior to receiving final acceptance.
Post-clearance Data	- data must be provided to BGTD in accordance with the conditional approval of a submission.
Review Clarifax	- the scientific/clinical review of a submission requires additional clarification to expand on, add precision to or re-analyse existing information or data in the submission.
Screening Clarifax	- the screening process has identified quality and/or regulatory issues within the submission.
Screening-Deficiency Notice	- deficiencies are identified during screening of original information and material that preclude continuation of the review.

Submission-Related Correspondence	**Issued when…….**
Submission-Closed Letter	- all items identified in an Acceptable with Conditions Letter are considered resolved
Unacceptable Letter - includes Licence Applications, Licence Amendments and Notices	- the screening or review of a submission is complete and the submission remains unacceptable from a regulatory and/or scientific perspective. All outstanding deficiencies/issues will be identified.

Appendix H

Biologics and Genetic Therapies Directorate

Fax-back Notification for Refiling a Rolling Submission

Submission Control Number: _____

Submission Title: _____

Submission Sponsor: _____

Sponsor Tracking Number: _____

A. To be completed by the submission sponsor

1. All correspondence related to the Notice identified above, provided to BGTD between [*Date submission received*] and [*current date*], is cross-referenced to the current application and should be considered for the current submission.

2. All information and material included in this submission and any additional information or material filed to amend this submission is accurate and complete and any reports and summaries correctly represent the information and material referred to or included in the submission are not false or misleading; or contain omissions that may affect its accuracy and completeness. We certify that the proposed procedure does not contain any step that may introduce changes or variations to the method prescribed by the manufacturer.

_____	_____	_____
Officer Responsible, Signature	Print Name	Date

B. To be completed by BGTD

1. The information and material cross-referenced above is considered acceptable for review.

2. The 90-day review default is identified as [*date this fax-back signed by sponsor + 90 days*]

_____	_____	_____
Officer Responsible, Signature	Print Name	Date

Appendix I
Biologics and Genetic Therapies Directorate
Fax-back Notification - Category II Submissions

(To be completed by BGTD)

Submission Control #:_____

Submission Document #:_____

Date of Receipt:

(To be completed by the submission sponsor)

Manufacturer:_____ **Establishment Licence #:**_____

Sponsor Tracking Number (If applicable):_____

Submission Title:_____

Submission Certification:

The information and data provided in support of this submission are complete and accurate and, where summarized, the summary correctly represents the information and material to which it refers.

_____ _____ _____

Officer Responsible, Signature **Print Name** **Date**

Fax-back to:_____**Fax No.:** _____

(To be completed by BGTD)

☐ Acceptable
☐ Not Acceptable (Rationale appended)
☐ Not Acceptable - Change of Category (Refiling Required) Letter included
☐ Change of Category - Letter included
☐ Clarification Sought - See appended telephone record

_____ _____ _____

Officer Responsible, Signature **Print Name** **Date**

(To be completed by BGTD)

Date Submission Accepted for Review:_____

Date Fax-back Complete (BGTD): _____

Signature:_____

Biologics and Genetic Therapies Directorate
Fax-back Notification - Category II Submission

BGTD Control #:_____

Description of Change (Submission sponsor to fill in the appropriate section)

A. Work Instruction Revisions	
Work Instruction Identification Number	
Work Instruction Title	
Description of Revision(s)	
Rationale for the Change	
Risk Assessment	
B. Equipment Changes	
Equipment Identification	
Manufacturer/Model Number	
Description of the Change	
Rationale for the Change	
Risk Assessment	
C. Donor Screening	
Description of Change	
Rationale for the Change	
Risk Assessment	
D. Contractor Change	
Contractor being Eliminated	
New Contractor	
Function of Contractor	
Rationale for the Change	
E. Changes to Facilities	
Description of Change	
Rationale for Change	

F. Label Change (Note: Provide a copy of the proposed label)	
Change to Label	
Rationale for the Change	

G. Extension of Approved Changes to Subsequent Sites	
Description of Change	
Rationale for extending the change to a subsequent site	
Cross Reference to BGTD Control Number	
Work Instructions: - certification that the same process and work instructions are being used as was originally accepted by BGTD - identification of deviations from the BGTD accepted plan with a rationale for the change from the work instructions originally accepted by BGTD. - list of work instructions - training	
Proposed Implementation Date	
H. Other	
Change	
Rationale for Change	
Risk Assessment	
I. Additional Information Required for Each Submission	
1. Blood Banking Software Impacted	☐ Yes Provide Details ☐ No
2. Labels Impacted	☐ Yes Provide Labels ☐ No

Appendix J

Submission of Revised Work Instructions

In order to provide efficient review in a timely fashion it is important that changes made to the approved version of a work instruction are presented in a format that assists the review process. In most cases, only the changes made to a work instruction need be reviewed. These submissions must be provided as follows:

a. Appropriate changes from the approved version must be highlighted, including additions, deletions etc.

b. A change rationale, including relevant references (e.g. BGTD requirement), should be provided as an introduction to each revised work instruction, explaining why a change has been made. Any supporting documentation should be provided.

c. The revised work instruction should be linked to the previously approved work instruction (or work instructions where there has been an amalgamation). The work instruction, upon which the revised work instruction has been built, is referred to as the "Roadmap SOP(s)" and must be provided to facilitate the review.

d. If a revision to work instruction 001 requires re-writing SOP 002 or writing a new SOP 003 these linkages must be documented and all affected SOPs updated as required.

e. Any newly introduced SOPs or forms should be noted as such.

In cases where it has been necessary to completely re-write an SOP, it may be necessary to review the entire SOP and not just the changes made to the previously approved SOP - essentially they are reviewed as “new” SOPs. For each SOP revised in this manner a summary of the critical changes made and the rationale for these changes must be provided.