The BGTD Lot Release Program - The Current State of Affairs

Canadian Association of Professionals in Regulatory Affairs
Webinar March 25, 2015

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Canada

Why Does BGTD have a Lot Release Program?

- The Lot Release Program provides an additional check on biologic drugs to help assure their safety for human use.
- Since biologic drugs are isolated from, or manufactured using, living organisms, they are inherently more variable than chemically synthesized drugs and require additional regulatory oversight.
- Biologic drugs are sensitive to changes in the starting materials and manufacturing, and therefore difficult to consistently produce and characterize.




Lot Release Program: Legislative Authority

- The Lot Release Program derives its legislative authority from section C.04.015 of the *Food and Drug Regulations*

> *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*

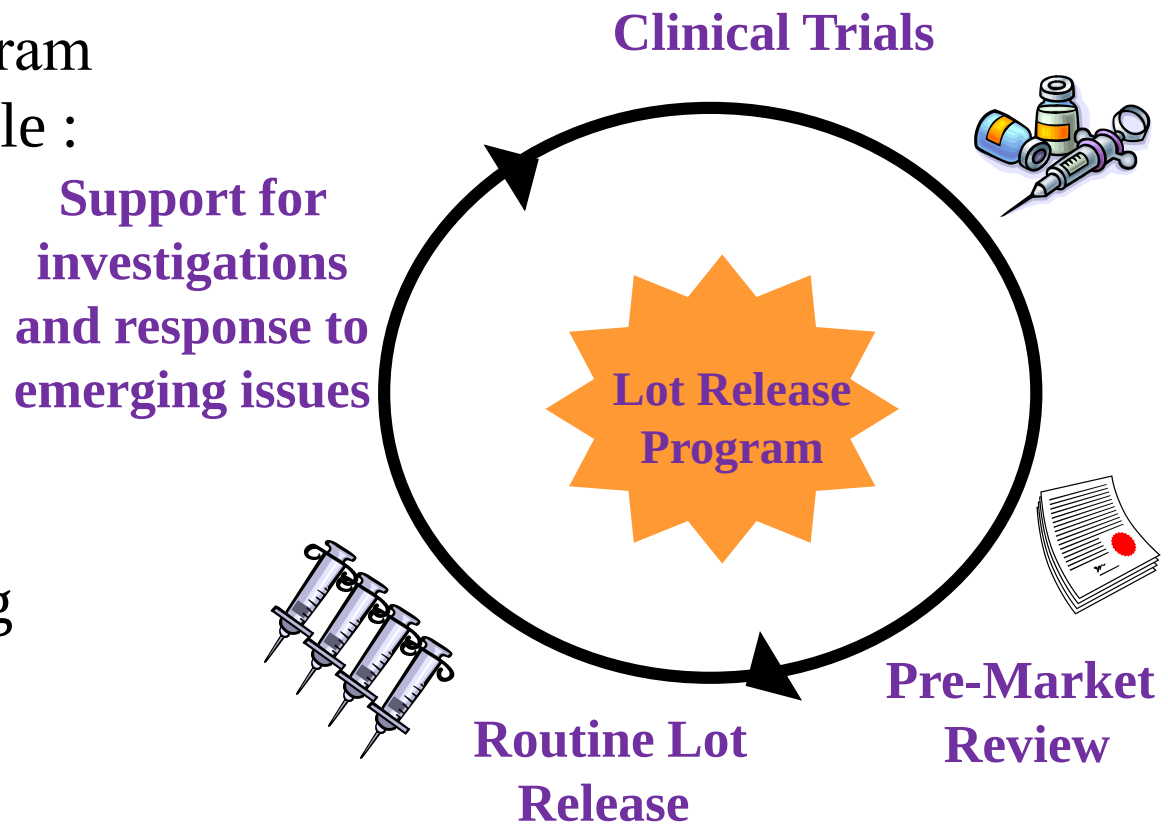
- Each lot of a Schedule D (biologic) drug is subject to the Lot Release Program before sale in Canada.




Lot Release: Life Cycle Approach

BGTD's lot release program spans the product lifecycle :

- Clinical Trials
- Consistency Testing
- Routine Lot Release
- Response to Emerging issues

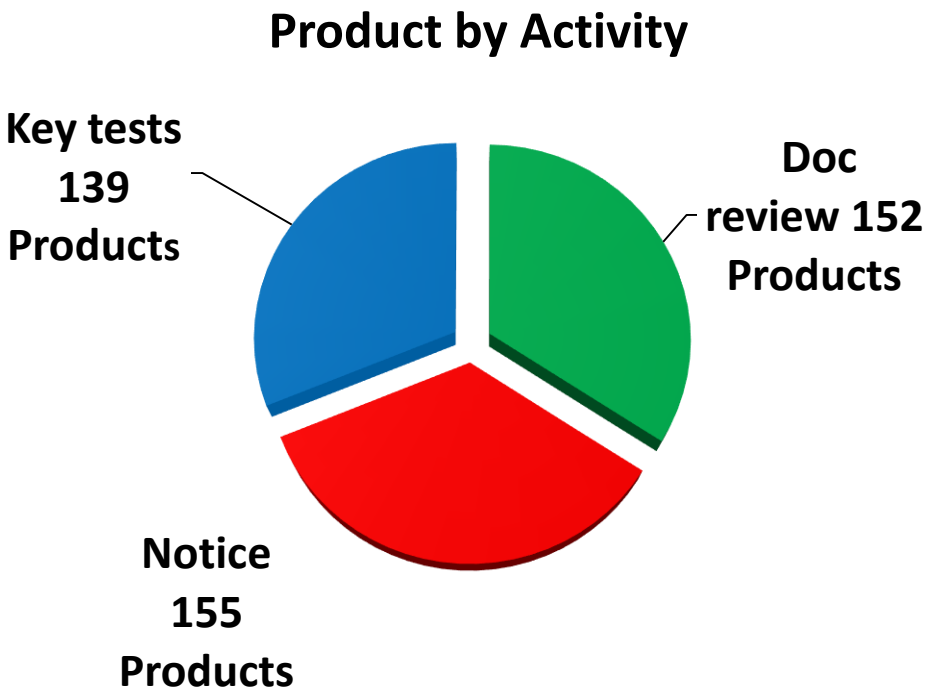


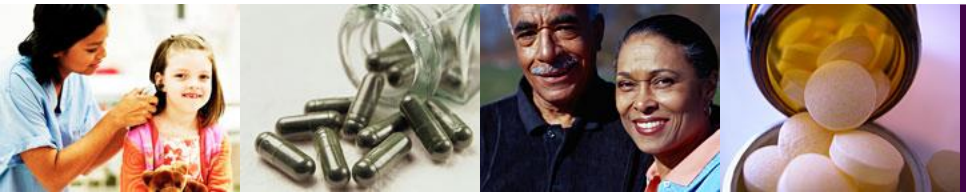



Lot Release: Risk-Based Oversight

While all Biologics on the Canadian market are within the scope of the lot release program, activities carried out range from:

- Receiving notifications only
- Document review only
- Document review and targeted testing





Evaluation Groups

Products are assigned to one of four Evaluation Groups, with each group having different levels of regulatory oversight based on the degree of risk associated with the product.

- Group 1A / 1B (pre-market only: clinical lots, consistency lots)
- Group 2 (lab testing and protocol review)
- Group 3 (protocol review)
- Group 4 (company informs BGTD of lots in the market)




Brief History

- **1996:** Review/Testing/Approval of Biologic Drug Lots (draft document)
- **2005:** Guidance for Sponsors: Lot Release Program for Schedule D (Biologic) Drugs published which introduced the following revised requirements:
  - Sponsors must submit a Yearly Biologic Product Report for all approved biologic drugs.
  - The Fax-back process for Group 4 products was expanded to include all Group 4 products, not just those containing Human-derived Excipients (HDE).




Group 1A: Clinical Trial Materials

- This Evaluation Group consists of clinical trial materials associated with authorized Clinical Trial Applications (CTAs).
- For prophylactic vaccines, the certificate of analysis (CoA) must to be submitted to BGTD for review (samples for testing may also be required). A formal release letter for use of the vaccine lot in the clinical trial is issued.
- For all other biologics, sponsors are required to complete and file a Fax-back form and await a signed response from BGTD prior to use of the clinical trial material.




Group 1B: Consistency Testing

- This Evaluation Group is intended for consistency samples associated with a New Drug Submission (NDS) or Supplemental NDS (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 a Notice of Compliance (NOC) is issued; a formal release letter is required from BGTD.




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. Samples of each lot along with the testing protocol must be submitted to BGTD.
- 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.




Group 3: Protocol Review and Periodic Testing

- Products requiring a moderate level of 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.
- BGTD reviews testing protocols but samples are not routinely submitted. Instead, at the discretion of BGTD, samples may be requested for Periodic Testing.
- 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.




Group 4: Notification and Periodic Testing

- Products in this Evaluation Group do not undergo sample testing or protocol review by BGTD.
- The manufacturer of that drug is required to notify BGTD via Fax-back 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.




Lot Release Program Summary (2013 Annual Report)

Lot Release Group	CERB			CBTE	CVE		Total
	Hormones and Enzymes	Cytokines and Growth Factors	Monoclonal Antibodies	Blood Products Division	Bacterial and Combination Vaccines	Viral Vaccines	
	Number of Lots						
1A Clinical Trials	Fax Backs			0	21	37	58
1B Consistency	23	14	15	24	8	3	72
2 Lot Release	0	0	0	371	100	186	657
3 Release on Protocol	606	74	20	262	86	15	801
4 Fax-Back	381	446	326	292	0	0	1445




Lot Release: Risk-Based Oversight

- Activities conducted are rationalized based on the available evidence (product history, use, evidence for consistent manufacture & testing) and documented under our quality management system.

- Activities are reviewed on an ongoing basis, and the level of product oversight changes as appropriate based on review of consistency of product quality or in response to emerging issues

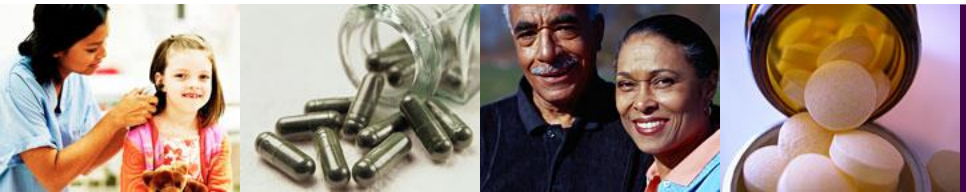
- Products which changed release groups in 2013:
  - Group 2 → 3 (15 products)
  - Group 3 → 4 (4 products)




Lot Release: Efficient use of Resources

Testing carried out focuses on key attributes (e.g. potency, purity) and various strategies are employed to optimize use of resources

- Periodic testing (e.g. lots tested on a quarterly basis)
- Testing of bulk lots instead of multiple packaged lots
- Use of foreign regulatory agency test data



Program Value:
Identifying and mitigating risk

The lot release program has allowed BGTD to identify and address concerns. Examples include:

- Testing for Biologics prior to product licensure
  - Leading to development of improved methods and better harmonization of quality control tests for new products globally
- Identifying specific lots prior to lot release that are not compliant with market authorization, pending commitments, or incorrectly labelled
  - Avoiding on market failure or recall situations




Program Value:
Identifying and mitigating risk (continued)

The lot release program has allowed BGTD to identify and address concerns. Examples include:

- Issues with product performance (adverse quality control issues / trends observed by BGTD during lot release)
  - Leading to discussions with manufacturers to resolve problem (e.g. manufacturing or assay/reference drift) before product failure




Program Value: Enabling Access

The lot release program has allowed BGTD to regulate products on a lot by lot basis, to enable or maintain essential products on the Canadian market in cases where:

- Incomplete information to support individual lots (exceptional event during manufacture or limited data available at time of authorization) is provided
- Issues are identified at manufacturing or testing sites which affect some or all of the lots
- Support other NRA in decision making regarding product access




Program Value:
Supporting International Markets

Canadian Lot Release is used support the international marketing of WHO prequalified influenza vaccines as well as other vaccines specifically produced for export.

Canadian Lot Release is used to support international marketing of Biologics made in Canada:

- Vaccines
- Blood Products
- Lung Surfactant




Program Value: International Regulation

Laboratory capacity is a key indicator of a mature regulator. Our lot release laboratories help form key links internationally through meaningful participation in:

- European and US Pharmacopoeial monograph development
- WHO Expert Committee Biological Standardization
- The Official Medicine Control Laboratories (OMCL) network
- International standardization activities for methods and reference materials
- Multilateral dialogues with other major regulators (EMA, FDA)




International Activities

- In 2012 BGTD joined the EDQM OMCL network as an associate member
  - Participation in the Annual Meeting closed session
  - Share information on lots submitted to the EU (BGTD is notified when a lot is rejected or withdrawn)
  - Access to EDQM databases
- Participation in many international collaborative studies




WHO Audit of Testing Activities for Pre-qualified Vaccines

- BGTD supports WHO in the vaccines prequalification process (review of dossier and product testing)
- In July 2013, WHO conducted an audit to review assay performance and supporting activities for the following vaccines:
  - BCG, Yellow fever, typhoid fever, measles, rubella, mumps and IPV




ISO 17025 Accreditation

- BGTD is currently accredited as conforming to ISO/IEC 17025:2005 by the Standards Council of Canada for the following activities:
  - Biological Testing Blood Products (6 test methods accredited)
  - Biological Testing Vaccines (8 test methods accredited)
  - Physicochemical Testing Blood Products (5 test methods accredited)

  A complete listing of the specific accredited test methods is available at https://www.scc.ca/en/palcan/990

- BGTD plans to enlarge the scope of the accreditation to include all assays used for lot release activities.



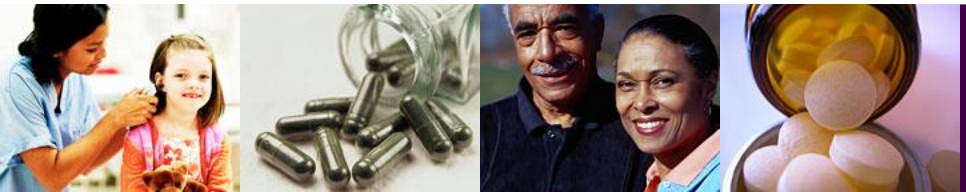

ISO 9001:2008 Certification

- As of March 4, 2015 BGTD received ISO/IEC 9001:2008 certification from the Canadian General Standards Board
- The lot release program was part of the scope of the certification.




Performance Monitoring of the Lot Release Program

- Conducted under the requirements of:
  - The BGTD quality management system-management review process (quarterly and annual reports)
  - The EDQM OMCL network (annual reporting)



Blood Products
Performance Monitoring for Groups 2 and 3

Period covered Jan 1, 2014 to Oct 24, 2014

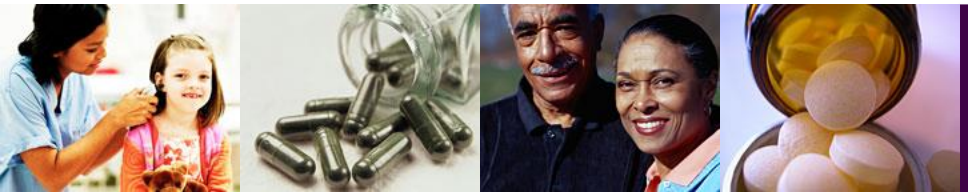
Summary	# of Lots	% of Lots
Lot release decisions	451	
Lots released	448	99.3%
Lots rejected	3	0.7%
Decisions within target timeframe	448	99.3%
Decisions exceeding target timeframe	3	0.7%




Viral Vaccines
Lot Release Performance Monitoring for Groups 2 and 3

Period covered Jan 1, 2014 to Oct 24, 2014

Summary	# of Lots	% of Lots
Lot release decisions	175	
Lots released	175	100%
Lots rejected	0	0.7%
Decisions within target timeframe	169	96.6%
Decisions exceeding target timeframe	6	3.4%



Bacterial and Combination Vaccines
Lot Release Performance Monitoring for Groups 2 and 3

Period covered Jan 1, 2014 to Oct 24, 2014

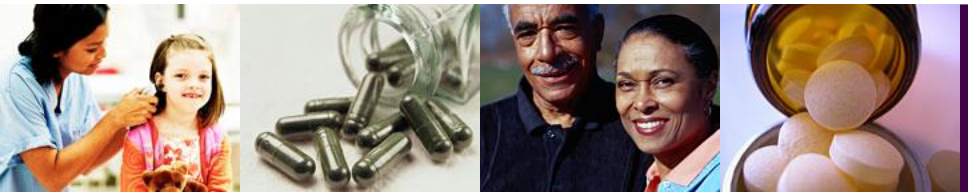
Summary	# of Lots	% of Lots
Lot release decisions	130	
Lots released	130	100%
Lots rejected	0	0 %
Decisions within target timeframe	126	96.9%
Decisions exceeding target timeframe	4	3.1%




Biotherapeutics
Lot Release Performance Monitoring for Groups 2 and 3

Period covered Jan 1, 2014 to Oct 24, 2014

Summary	# of Lots	% of Lots
Lot release decisions	469	
Lots released	467	100%
Lots rejected	0	0 %
Decisions within target timeframe	469	100%
Decisions exceeding target timeframe	0	0%



Performance Monitoring – Method Proficiency

- BGTD performs trend analyses (at least annually) for accredited test methods.
  - Trend analyses includes comparison between BGTD results and the manufacturer's results.
- Laboratory investigations are conducted where trends and/or repeated invalid test results are observed.
- Test method proficiency is reported annually under the BGTD quality management system and to the OMCL network (annual report).




Thank you