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Establishment of a Reliable Source of Blood and Blood Products in Canada

Dr. Francisca Agbanyo, Chief
Blood, Cells, Tissues and Organs Division
Centre for Biologics Evaluation
Biologics and Genetic Therapies Directorate
Health Products and Food Branch



Canada

Outline of Presentation

- Blood Safety: Role of Key Stakeholders
- Overview of the Canadian Blood Supply System
- Regulation of the Blood Supply System
  - The National Regulatory Authority
  - Canadian Regulatory Framework
- *Blood Regulations*
- *Food and Drug Regulations*
- Summary




Blood Safety: Role of Key Stakeholders




Blood Safety – A Shared Responsibility

Federal Government

- **Health Canada:** Administer the Food and Drugs Act and Regulations (i.e., Blood, Food and Drug and Medical Device Regulations)
- **Public Health Agency of Canada:** Responsible for National Surveillance for Communicable Diseases

Provincial/Territorial Governments

- Health Professionals/Authorities governing medical practice
- Hospitals that transfuse blood and report adverse reactions
- Public Health Authorities

SAFETY

Manufacturers

- Blood Establishments, Plasma Centres and Plasma Fractionators responsible for implementing safety standards

Other Players

- Donors disclosing risk factors
- Recipients reporting adverse reactions
- Non-Governmental Organizations




Canadian Blood Supply System




Blood Supply System -1

- Two not-for-profit blood establishments: Canadian Blood Services (CBS) and Héma-Québec (HQ)
  - Funded by the provincial/territorial governments
  - Recruit voluntary non-remunerated blood donors
  - Implement measures for donor deferral and testing
  - Process and store blood and blood components for transfusion and for further manufacturing into blood products
  - Implement Quality Management Systems to maintain the quality and safety of donated blood and blood components
  - Distribute blood components (red blood cells, platelets, plasma, cryoprecipitate, etc.) to hospitals for transfusion
  - Distribute Canadian plasma to foreign plasma fractionators for further manufacturing
  - Distribute blood products (albumin, Intravenous immunoglobulins, Hyper-immune globulins, coagulation factors, etc) manufactured from plasma obtained from either Canadian or foreign sources to hospitals




Blood Supply System - 2

- **Hospitals-Based Facilities**

  - Collection of **autologous blood** for transfusion
  - Storage of blood components in hospital blood banks
  - **Transformation** of blood components determined to be safe for transfusion by CBS and HQ prior to distribution to hospitals
    - ✓ Irradiation
    - ✓ Washing
    - ✓ Pooling




Blood Supply System-3

- **Two for-profit plasma collection centres**
  - **Recruit paid donors**
  - **Collect plasma for futher manufacturing into blood products**
  - **Apply the same measures as CBS and HQ for donor screening, testing, plasma collection, storage and distribution**
- **Domestic Plasma fractionator (manufacturing of plasma derivatives from specialty human plasma, e.g., RhoD immune globulin, hepatitis B immune globulin, etc)**
- **Foreign Plasma fractionators**




Adequacy of Supply

- **Self Sufficient in Blood Components for transfusion**
  - Activities carried out solely by not-for-profit Canadian blood establishments (i.e., large stand-alone blood establishments or hospital-based blood banks)
  - Use of only voluntary non-remunerated blood donors
- **Adequacy of Blood Products achieved by**
  - Use of Not-for-profit and for-profit Canadian plasma centers
  - Use of voluntary non-remunerated and paid Canadian blood donors
  - Use of foreign and domestic fractionators of Canadian plasma
  - Purchase of additional blood products from commercial sources that are manufactured mostly with plasma from paid donors
  - Use of recombinant coagulation factor VIII for hemophiliac patients
- **Regulatory oversight is essential for maintaining the safety/quality/efficacy of products from these various sources**

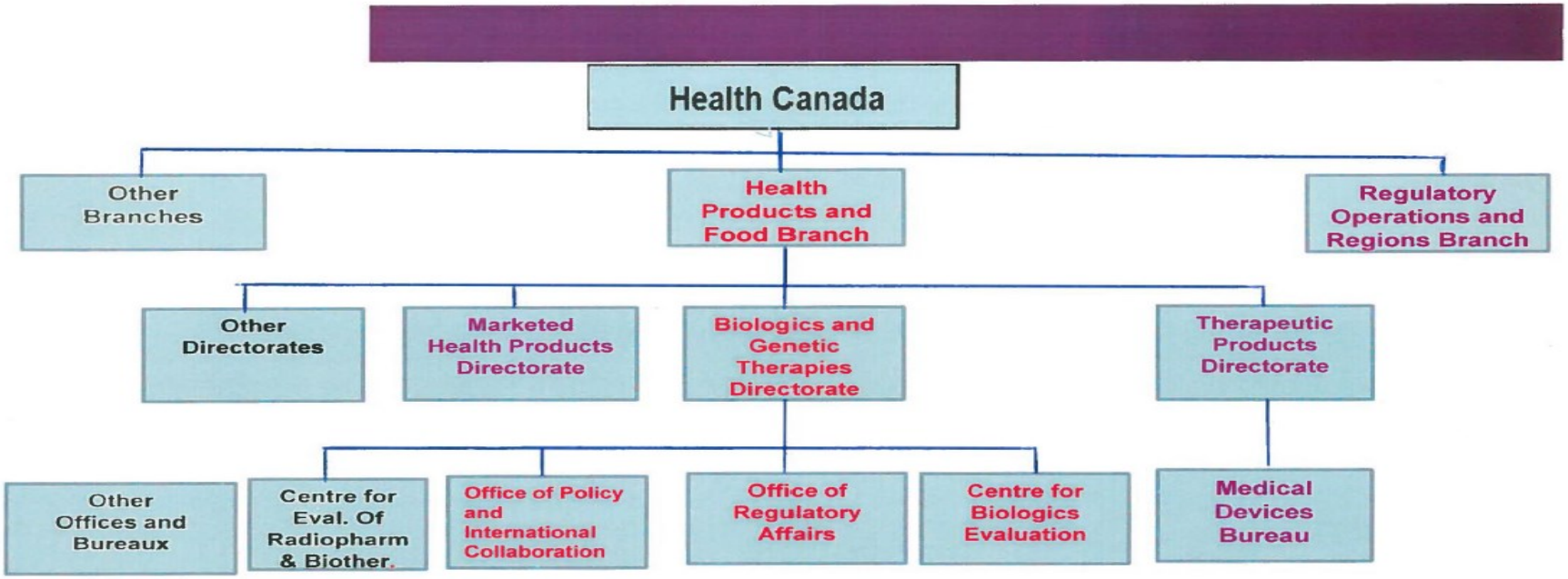



Regulation of the Blood Supply System




The National Regulatory Authority (NRA)

- **Health Canada** is the federal government health department responsible for regulating blood components and blood products
- Independence of Health Canada from regulated parties



Key Players in Health Canada

- **Health Products and Food Branch (HPFB)**
  - **BGTD:** Regulatory activities such as:
    - ✓ Development of regulations, standards, etc.
    - ✓ Submission management
    - ✓ Submission review (blood components, blood products, anticoagulants and preservation solutions), etc.
  - **MHPD:** Post-market activities such us drug safety surveillance, collection of adverse events data and risk/benefit assessment
  - **TPD/MDB:** Regulation of in vitro diagnostic test kits, blood collection equipment, blood bag systems, etc.
- **Regulatory Operations and Regions Branch (RORB)**
  - Establishment Licensing (EL) and Compliance and enforcement activities such as inspections and investigations
- Use of **Expert Advisory Committees** when necessary




Canadian Drug Regulatory Framework

- **Statutes (Acts):** provides scope, and legal authority to make regulations
- **Regulations:** developed under the authority of the Act for different types of products -- interpret the Act and provide policies/standards having the force of law
- **Policies/Guidelines/Guidance:**
  - Interpret and provide details on how to meet the regulations
  - Allow flexibility and adaptation to change, faster and simpler to introduce than Regulations
  - They are not legally binding and cannot contradict or override regulations
- **Directives:** Address emerging issues (e.g., vCJD, leukoreduction) or specify technical requirements




Relevant Canadian Laws and Regulations

- **Statute/law: The Food and Drugs Act**

- **Regulations developed under the Act**
  - ***Blood Regulations* (effective October 2014).**
    - ✓ **Blood components for transfusion or further manufacturing**
  - ***Food and Drug Regulations (FDR)***
    - ✓ ***Pharmaceutical and Biological Drugs (including blood products, anticoagulants and preservation solutions)***
  - ***Medical Devices Regulations***
    - ✓ ***In vitro* diagnostic test kits, blood collection equipment, blood bag systems, etc.**




Blood Regulations




New Regulations for Blood Components

- **Blood components were subject to the *Food and Drug Regulations* until 2014**
- **Why new stand-alone *Blood Regulations* were introduced in October 2014?**
  - **There were no specific requirements in the *Food and Drug Regulations (FDR)* for blood components for transfusion, therefore various guidelines/guidance were used to supplement these regulations**
  - **Procedures for processing and storage of blood components are well established, therefore some requirements in the FDR were not applied because they were deemed too stringent**
  - **To consolidate all relevant requirements for blood components (make the regulations user-friendly)**




Blood Regulations

- **Blood Regulations specify requirements for blood components for transfusion and further manufacturing**
- **The Regulations are Standards-Based**
  - **They reference sections of the Standards for Blood and Blood Components (*CAN/CSA-Z902-15)* developed by the Canadian Standards Association (CSA), thus giving these sections the force of law**
    - ✓ **Standards developed by experts and stakeholders through a consensus-driven process**
    - ✓ **Subject to public consultation**
    - ✓ **Revised more frequently than regulations to keep current with technological advancements and emerging threats**
  - **Some sections of the CSA Standards that are not referenced in the *Blood Regulations* may be cited in Guidance as recommended practices.**




Scope and Application of Blood Regulations

- Apply to human blood collected for transfusion and for further manufacturing
- Apply to all establishments that perform regulated activities, including hospitals
- The Regulations are accompanied by a Health Canada Guidance Document that explains the regulatory requirements

- **Note:** Blood components are used for clinically proven therapies and typically do not require clinical trials. However, new blood components that are not used in Canada during standard medical practice may still be subject to clinical trials under the *Food and Drug Regulations*




Activities Covered in the Blood Regulations

- Processing
  - Donor suitability assessment
  - Collection and Testing
  - Blood component preparation
- Labelling, storage, distribution
- Transformation (washing/pooling/irradiation of components after they have been determined safe for use)
- Exceptional distribution
- Pre-Assessed Donor Programs (PADP)
- Importation under urgent circumstances
- Quality management System (use of standard operating procedures, facility, equipment, personnel, adverse events and error/accident investigation and reporting, records, etc.)
- Powers of inspectors




Risk Classification for Regulated Activities

- **High risk activities:** processing or importation of allogeneic blood
- **Medium risk activities:** collection of autologous blood, transformation, and Pre-Assessed Donor Program
- **Lower risk activities:** storage, labelling, distribution, adverse events and error and accident investigation and reporting, etc.




Regulatory Tools (1)

❖ High Risk Activities

- **An Authorization and Authorization Amendment to give establishments the authority to perform these activities.**
  - ✓ **This requires a pre-market review of blood submissions and may require an on-site evaluation of the manufacturing process.**

- **An Establishment Licence (EL) to allow establishments to conduct activities requiring a licence in a building which has been assessed to be compliant with their Authorization, Authorization Amendment and Regulations.**
  - ✓ **This requires an inspection during the review of the EL application and may require an inspection for a licence amendment**



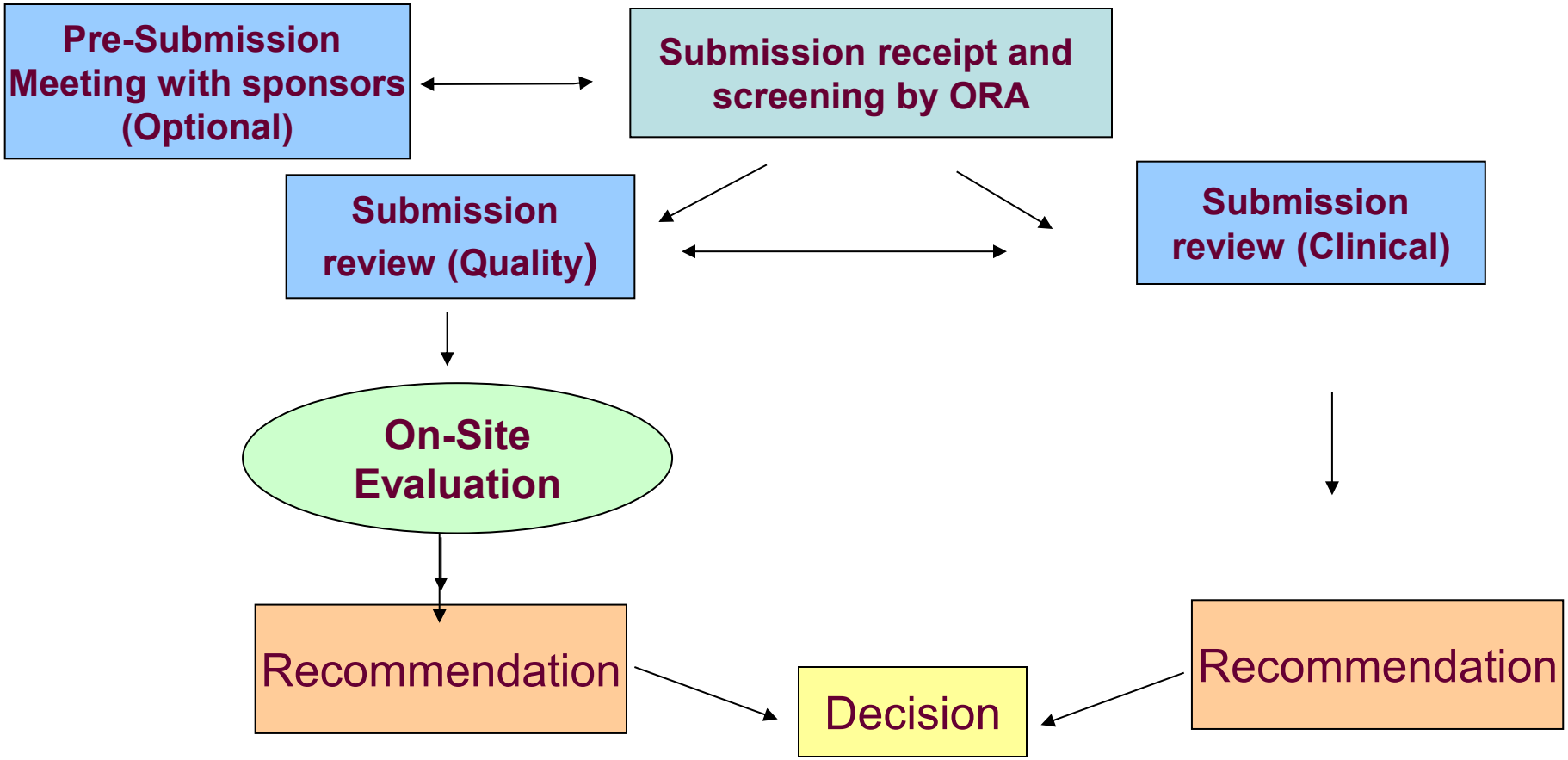

Regulatory Tools (2)

- **Medium Risk Activities**
  - **A Registration**
    - ✓ **Requires an attestation to compliance with the Regulations and an annual statement of compliance**
- **Lower Risk Activities**
  - **Compliance with applicable regulatory requirements**
  - **No requirement for an Authorization, an EL or a Registration**
- **Inspection Program**
  - **Scheduled inspections of licensed and registered establishments by Health Canada to verify compliance with regulations.**
- **Surveillance Program**
  - **Collection and analysis of adverse reaction data**




Submission Review Process

Overview: Notice of Authorization and Amendments






Food and Drug Regulations




Applicable Requirements of the FDR (1)

- **All drugs, including biologics, are regulated under the *Food and Drug Regulations* (Part C, Divisions 1, 1A, 2, 4, 5 and 8)**
  - **Division 1: Prohibitions and general requirements applicable to drugs (examples include requirements for labelling, Drug Identification Number, adverse events reporting, product recalls).**
  - **Division 1A: Establishment Licensing (must comply with Divisions 2 and 4)**
  - **Division 2: Good Manufacturing Practices (GMP)**
  - **Division 4: Schedule D drugs (Biologics)**
  - **Division 5: Clinical Trials**
  - **Division 8: New Drugs**
- **Several guidance documents and policies relating to Biologics**




Applicable Requirements of the FDR - 2

- **Division 4**
  - **Specifies additional/specific requirements for different biological drugs listed in Schedule D to the Act (list includes, among others, drugs that are made from blood, drugs derived from recombinant DNA procedures).**

    Note: Blood and blood derivatives, and human plasma collected by plasmapheresis have been removed from Schedule D (effective October 22, 2014)

  - **Requires submission of testing protocols and drug samples to Health Canada**




Applicable Requirements of the FDR - 3

- **Division 5 (Clinical Trials)**
  - **"Clinical trial" means an investigation in respect of a drug for use in humans that involves human subjects and that is intended to discover or verify the clinical, pharmacological or pharmacodynamic effects of the drug, identify any adverse events in respect of the drug, study the absorption, distribution, metabolism and excretion of the drug, or ascertain the safety or efficacy of the drug.**
- **Division 8 (New Drugs)**
  - **a drug ……that has not been sold as a drug ……. in Canada for sufficient time and in sufficient quantity to establish in Canada the safety and effectiveness of that substance for use as a drug**




Content of Clinical Trial Application (CTA)

❖ Some Key Requirements

- A protocol describing the objectives, design, methodology, statistical considerations and organization of the trial
- An Investigator's Brochure containing the preclinical data and clinical data (if available) on the drug
- A patient informed consent form that states the risks and anticipated benefits
- Approval by Research Ethics Board
- Chemistry and Manufacturing information on the drug
- Information on human-sourced excipients
- Compliance with Good Clinical Practices (GCP) and Good Manufacturing Practices (GMP)
- Reporting of serious unexpected adverse drug reactions
- Etc., etc.,




Chemistry and Manufacturing (C&M)

- **Some Key C&M Requirments**
  - ✓ **Controls of starting raw materials (donor material)**
  - ✓ **Control of ancillary reagents/excipients used in manufacturing**
  - ✓ **Manufacturing process and controls**
  - ✓ **Product characterization and specification**
  - ✓ **Validation of analytical methods, processes, shipping, equipment**
  - ✓ **Stability and shelf life**
  - ✓ **Equipment and facilities**
  - ✓ **Adherence to Good Manufacturing Practices**
  - ✓ **Etc.**




Pre-Clinical Requirements

- **Pre-Clinical Studies**
  - **Preliminary proof of concept to support further clinical development**
  - **Use of appropriate animal models**
  - **Assessment of dosage, route of administration, timing of product administration, etc.)**
  - **Assessment of efficacy**
  - **Adverse events monitoring (e.g., tumorigenicity, Immunogenicity, biodistribution, etc.)**
  - **Adherence to Good Laboratory Practices**




Clinical Studies

- **Clinical Studies Trial design (early/late phases)**
  - Inclusion/exclusion criteria
  - Data analysis
  - Safety monitoring expectations (duration of follow-up and adverse events monitoring)
  - Ethical expectations and standards (informed consent), Etc.

- **Risk management plan (RMP)**
  - All risk information gathered on the product during its global use in humans (clinical trials, off label use, marketed use, all indications and dosage forms, etc.)
  - Safety surveillance plan (i.e. gathering of additional safety information)
  - Monitoring the efficacy of the proposed plan and activities
  - Etc.




Content of New Drug Submission

- Drug submissions are filed upon completion of Clinical Trials
- Include data (chemistry and manufacturing, non-clinical and clinical) to support product safety and efficacy
- Must be approved by Health Canada prior to marketing



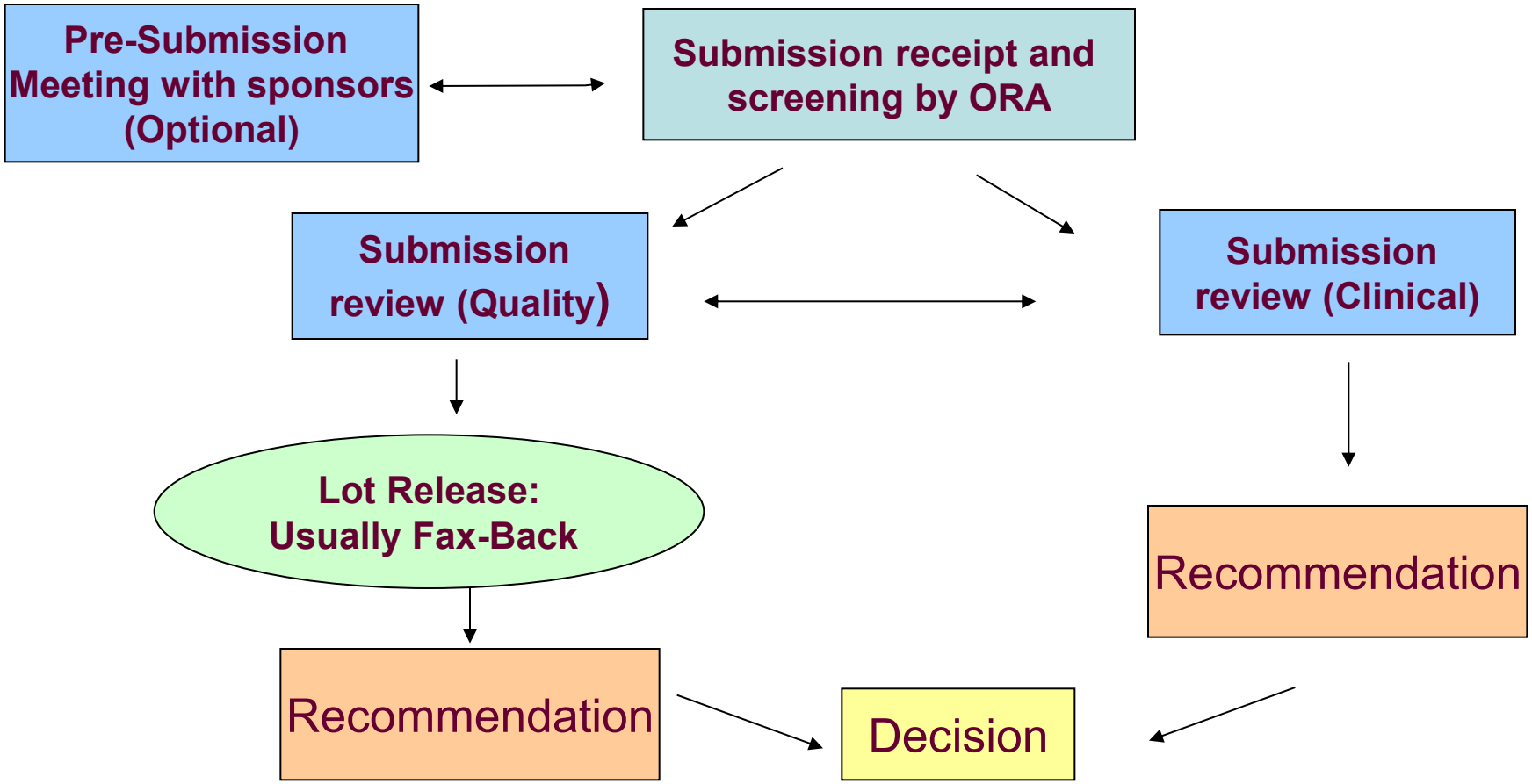

Risk Assessment of Biologics

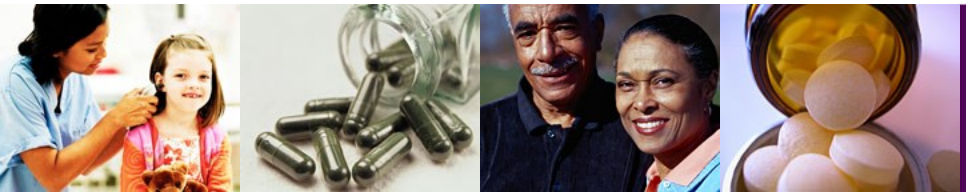
- **Risk Assessment – three main elements**
  - **Paper review of manufacturer's drug submissions containing manufacturing, non-clinical and clinical data**
  - **Lot-Release**
    - ✓ **Laboratory work on samples received from drug companies to confirm potency/purity/safety**
  - **On-Site Evaluation (OSE) - for New Drug Submissions**
    - ✓ **Assessment of the production process and facility for a specific product which ensures that the manufacturing process conforms to information described in the submission**




Review Process for Biologics (CTAs)

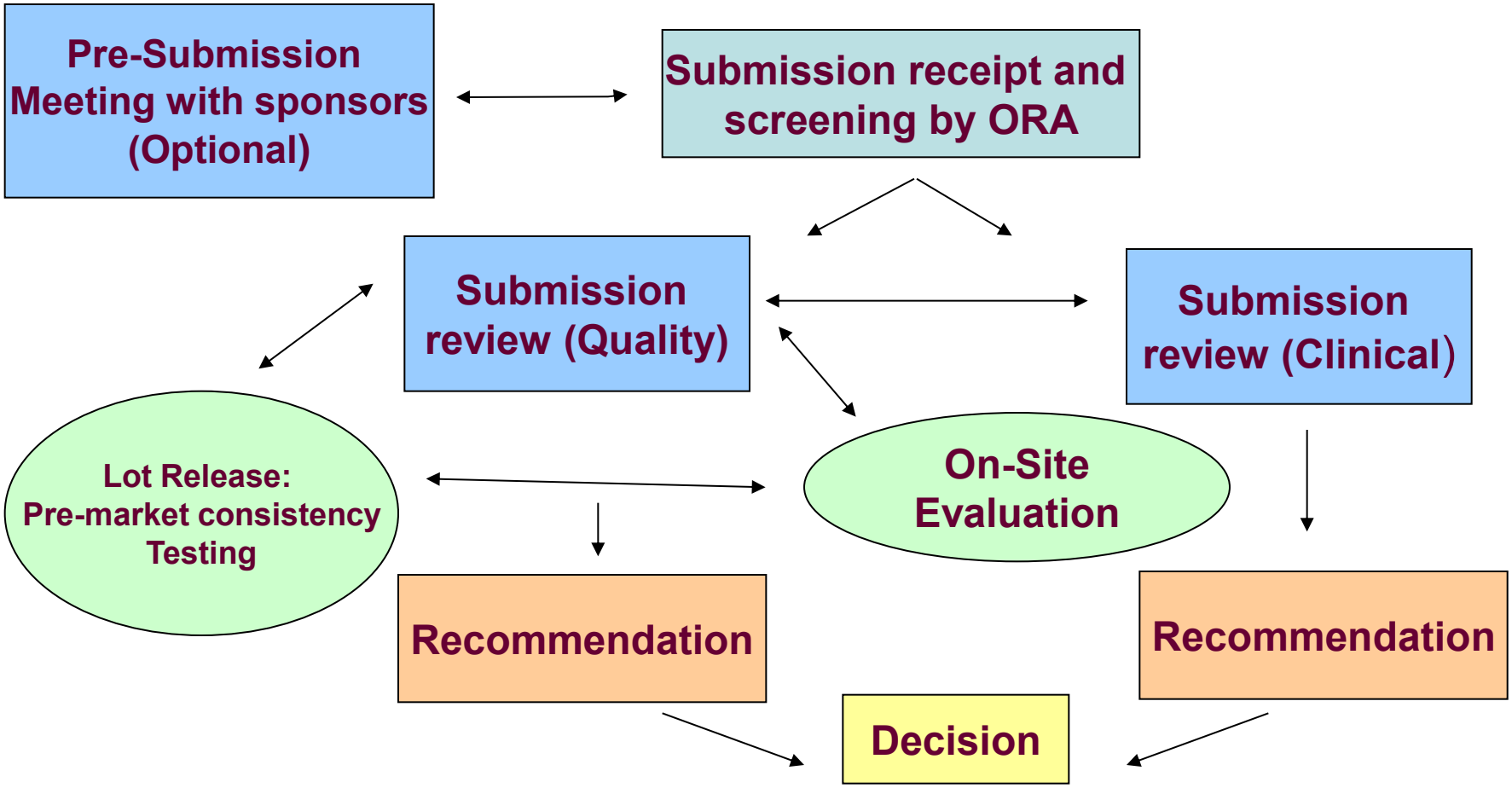
Overview: Clinical Trial Application (CTA)

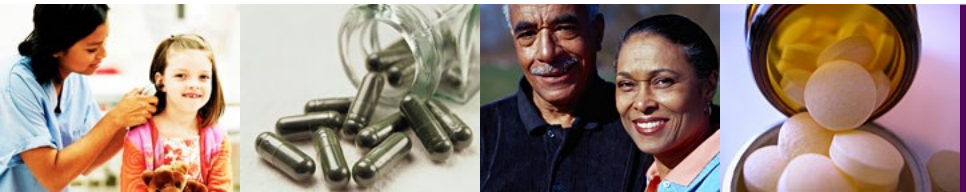




Review Process for Biologics (NDS)

Overview: Premarket Review for New Drug Submission (NDS)





Satisfactory Review Outcomes

- No Objection Letter (NOL) for CTAs
- Notice of Compliance (NOC) / market authorization for New Drug Submissions
- EL for manufacturing sites and importers based on provision of evidence to demonstrate GMP compliance




Post-Market Activities

- **Risk-Based Lot-Release Program:**
  - **Lot-by Lot Release**
  - **Laboratory testing of samples received from drug companies to confirm potency/purity/safety; and/or protocol review based on level of risk**
- **Review of manufacturer's drug submissions when changes are made to approved processes and procedures (Notifiable Changes)**
- **Submission of Yearly Biologic Product Report (YBPR)**
- **Analysis of adverse events data**
- **Compliance and enforcement activities**
- **Etc.**




Summary

- Canada is **self sufficient in blood components** for transfusion: obtained from voluntary non-remunerated blood donors and prepared by Canadian establishments
- The standards-based, risk-based approach recently employed for regulating **blood components** has made it possible to regulate all relevant establishments regardless of the level of risk associated with the activities they perform.
- Unlike blood components, **blood products** are derived from plasma: collected from both non-remunerated and paid donors; collected at Canadian and foreign plasma centres; and manufactured by Canadian and foreign plasma fractionators
- The regulation of blood components and blood products at the national level ensures uniform standards are applied regardless of the source of blood components or the location of the manufacturing site, and enhances their safety, quality and availability.




Enquiries Regarding Canadian Drug Submission Requirements, Contact

Office of Regulatory Affairs
Biologics and Genetic Therapies Directorate
1st Floor, Building #6
100 Eglantine Driveway
Address Locator 0601C
Ottawa, Ontario
K1A 0K9
Fax: 613-941-1708
Email: BGTD_RAD_Enquiries@hc-sc.gc.ca




Thank You For Your Attention

Questions?