Health Canada Santé Canada

Canada

Health Canada Requirements for Errors, Accidents and Adverse Reactions under the Blood Regulations

Biological Product Compliance Program

Health Canada

YOUR HEALTH AND SAFETY... OUR PRIORITY.

Overview

- Scope of the *Blood Regulations*
- Error/accident (E/A) Investigation and Reporting to Health Canada
  - E/A Examples
- Adverse reaction (AR) Investigation and Reporting to Health Canada
  - AR Examples
- Questions

Scope of the Blood Regulations

- Made under the authority of the *Food and Drugs Act*
- They apply to all persons or establishments that process, label, store, distribute or transform blood for transfusion or for further manufacture into a drug for human use, including establishments that import blood for transfusion

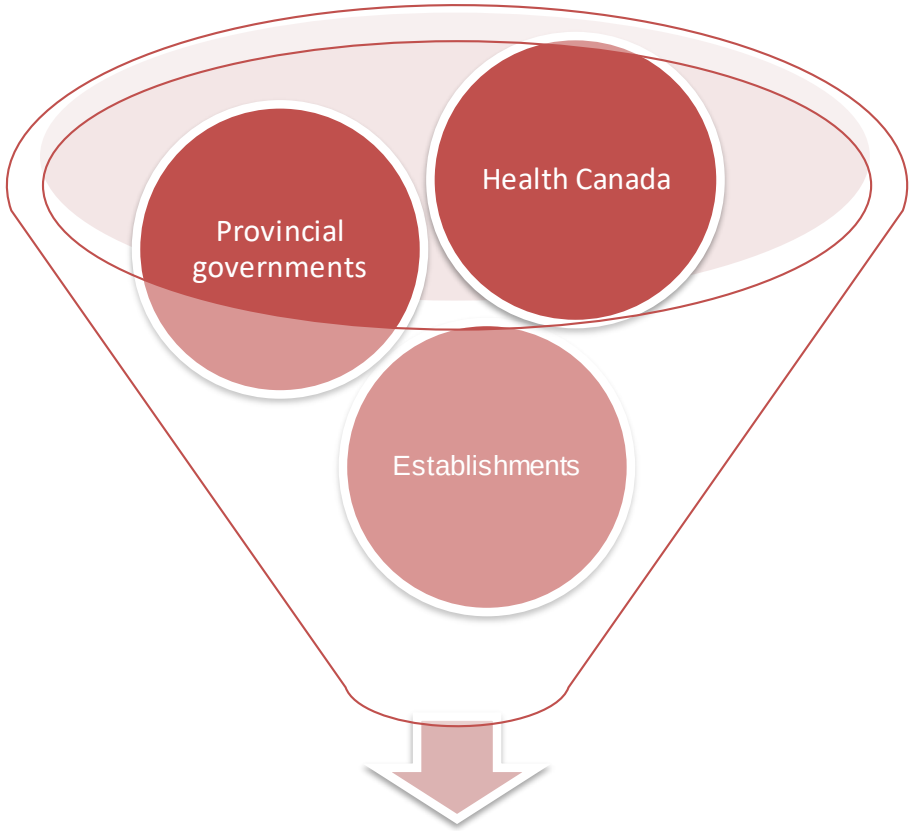
Regulated activities include:

Non-exhaustive list

- Processing (donor suitability assessment, collection, component preparation)
- Blood transformation (washing, irradiation, pooling)
- Distribution within or outside the hospital
- Plasma reduction (of platelets and red blood cells)
- Thawing
- Preservative depletion
- Aliquoting
- Any other activity that may impact the safety of the blood

The Blood Regulations **DO NOT** apply to the practice of transfusion medicine

Blood safety is a shared responsibility



Error and Accident Investigations and Reporting to Health Canada

Sections 103–108

Errors and Accidents (E/A) Overview

sections 103 to 108

- All establishments must comply with regulatory requirements for errors/accidents (E/As)

Including unregistered blood banks

- In the event of an error/accident, the blood establishment must (as applicable):
  - identify and quarantine the implicated blood
  - notify
  - investigate
  - report to Health Canada
  - cooperate and communicate

Only if the three criteria are met

Definitions under the *Blood Regulations*

Error – deviation from the operating procedures or applicable laws that could compromise human safety or the safety of blood

Non-irradiated blood component labelled as irradiated

~~Box not checked on order slip~~

Accident – an unexpected event that is not attributable to a deviation from the operating procedures or applicable laws and that could compromise human safety or the safety of blood

Blood bags with micro-leaks that are undetectable during visual inspection

~~Dropped blood unit that bursts~~

Human safety – the safety of donors and recipients of blood, in so far as it relates to the safety of the blood

Definitions under the *Blood Regulations*

Distribution – does not include transfusion

There is distribution when blood is determined safe and sent to another establishment or within an establishment for storage or transfusion. For example:

- An establishment sends blood to another establishment, including:
  - Blood from the collecting establishment's inventory is sent to a hospital
  - Hospital A sends blood to Hospital B

Even if the hospitals are under the same health authority with the same QA system and SOPs

- A blood bank sends blood in a refrigerator or cooler-type container within the same establishment for temporary storage before transfusion (e.g., the operating room or a patient's bedside on a ward)
- Blood is sent from a blood bank to a patient for transfusion

Blood is not considered to have been distributed when it is ready to be distributed and still in storage at the blood bank and remains in their control

E/As under the Blood Regulations

In the event of a potential E/A (or incident), the establishment must determine if the E/A:

- could compromise the safety of the blood
- occurred in the course of a regulated activity

If it is the case, this incident is considered an E/A under the *Blood Regulations*

Regulated activities include, but are not limited to:
Labelling; Storage; Distribution within or outside the hospital; Blood transformation (e.g.: pooling); Plasma volume reduction (of platelets and red blood cells); Thawing; Preservative depletion; Aliquoting; any other activity that may impact the safety of blood

Incidents outside the scope of the Blood Regulations

- Incidents involving **medication produced from blood** (blood derivatives)
- Incidents related to the **practice of transfusion medicine**, including collecting samples from patients, cross-match testing and blood transfusion
- Incidents during the **preparation of an order,** such as distribution of wrong blood to a patient or to another hospital

Examples of Incidents outside of the scope of the Blood Regulations

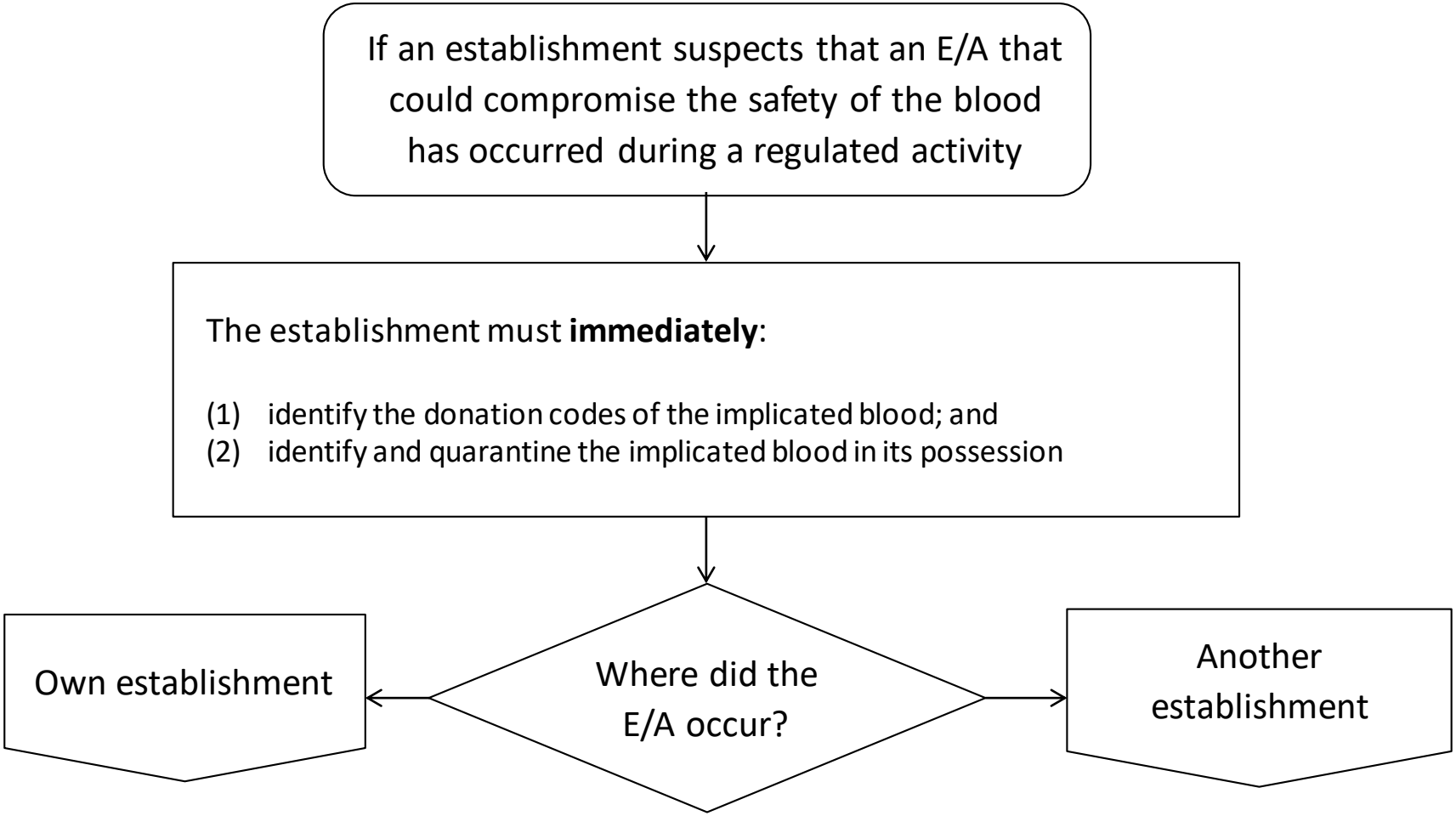
- Incident while collecting or managing patients' blood samples
- Incident while testing patients' blood before the transfusion (blood type and phenotype)
- Incident while testing received blood to confirm ABO/Rh group
- Incident during cross-matching
- Distribution of wrong blood (wrong blood type or component)
- Irradiated blood ordered but non-irradiated blood sent (blood correctly labelled as non-irradiated)

If the blood was not irradiated but labelled as irradiated, this would be an error under the Regulations

- Unit of blood transfused into wrong patient
- Unit of blood transfused too slowly or too quickly
- Hospital service delivery standards not met
- Transfusion of expired blood

If the blood was already expired when distributed by the blood bank, this would be an error under the Regulations

E/A Investigation and Notification



E/A of another establishment

section 103

After identifying the donation codes and quarantining the implicated blood, the establishment must notify:

- the establishment that collected the blood
- the establishment from which the implicated blood was received, if different
- any establishments to which it distributed the implicated blood

The notice must include the following information:

- Donation codes of the implicated blood
- Name of the implicated blood components
- The reason why the establishment suspects the safety of the blood was compromised

If the information was communicated verbally, a written notice must be sent as soon as possible

Establishments notified of the E/A must immediately quarantine the implicated blood in its possession and notify any establishment to which it distributed the implicated blood

Important to cooperate with the establishment conducting the investigation!

E/A at your own establishment

section 104

After identifying donation codes and quarantining blood

Sufficient evidence to conduct an investigation?

No

- Document reasons for not conducting investigation
- Notify establishment from which notice was received of decision, if applicable

Yes

- Initiate investigation
- Notify any establishment to which it distributed implicated blood

The notice must include the following information:

- Donation identification codes
- Description of the suspected E/A and an explanation of how the safety of the implicated blood may have been compromised

If the information was communicated verbally, a written notice must be sent as soon as possible

Is there sufficient evidence to conduct an investigation?

What does that mean?!

If no investigation conducted, important to document rationale

If you discovered or were notified of an incident (suspected E/A), you must conduct an assessment to determine if regulated activities were involved at **your** establishment and if the safety of the blood could be compromised.

Scenario

- You received blood from the collecting establishment and immediately sent the unopened container to another hospital.
- The other hospital notifies you that the blood appears to have not been stored at the proper temperature during transport.
- You conduct an assessment to ensure the transport container was not opened and was immediately sent to the other hospital within the required time limit.
- Conclude the activities that you carried out were not implicated. **Therefore, you do not have sufficient evidence to conduct an investigation.** The collecting establishment will conduct the investigation after you have informed them of the situation.

E/A Investigation and corrective actions

- An investigation may be simple or complex and may require an examination of multiple aspects in order to identify the full extent of what happened

- An investigation must include a root cause analysis and implementation of corrective and preventive measures (CAPA) in order to mitigate risks and prevent reoccurrence

- CAPA may include, but are not limited to:
  - new training for staff
  - review of procedures
  - additional verification steps
  - changes to processes

Detailed record of all actions taken

- CAPA must be implemented in a timely manner and their effectiveness must be evaluated thereafter

section 105

E/A Investigations - Cooperation and communication

When an E/A occurs at another establishment:

- The blood bank must communicate and cooperate with the establishment conducting the investigation by providing, upon request, relevant information or documents in its possession regarding the implicated blood
- The blood bank must provide relevant information or documents in its possession to all other affected establishments and inform them of the progress of the investigation

When an E/A occurs at your own establishment:

- The blood bank must have processes in place to provide relevant information on the progress of the investigation in a timely manner to all other affected establishments

When it is not clear which establishment must conduct the investigation, it is important to communicate and cooperate with all other affected establishments before concluding that an investigation is not warranted and before determining the disposition of the implicated blood

If the information was communicated verbally, a written notice must be issued without delay

E/A Investigation results

section 106

- The establishment conducting an investigation must notify in writing each establishment to which it distributed implicated blood of the investigation results and measures to be taken, if applicable.

- The notified establishment must forward the notice to all establishments to which it distributed implicated blood.

Scenario

- Hospital A sends blood to Hospital B during a patient transfer.
- Upon receiving it, Hospital B notices that the blood is too warm and that there are too few ice packs in the transport container. Hospital B must notify Hospital A.
- Once the investigation is completed, Hospital A must inform Hospital B of the investigation results, e.g., error during packaging (in the packaging configuration or employee error during packaging) or during delivery (delays)

Reporting E/As to Health Canada

section 107

The establishment must determine if all of the following criteria are met:

- ✓ Did the E/A occur during an activity conducted by the establishment?
- ✓ Was the E/A identified after the blood was distributed or transfused?
- ✓ Is there a reasonable probability that the E/A could have caused a serious adverse reaction if the blood had been transfused? This also applies when the blood has been transfused but did not cause any serious adverse reaction (however, a serious AR could have occurred)

If all of the above three (3) criteria are met, the establishment must submit a report to Health Canada:

- **Within 24 hours** after the start of the investigation, a preliminary report (FRM-0337)
- **Within 15 calendar days** after the start of the investigation or on request from Health Canada, a written update on any new information, progress, and risk mitigation measures taken
- **On completion of the investigation**, a final report containing:
  - the results of the investigation
  - the final disposition of the implicated blood and the reasons that justified it
  - root cause analysis and infectious agents involved, if applicable
  - all measures taken and all changes to relevant processes

How to report E/As to Health Canada

Errors and Accidents are reported to Health Canada's Biological Product Compliance Program (BPCP) of the Regulatory Operations and Enforcement Branch (ROEB).

The Blood Error or Accident Investigation Preliminary Report Form (FRM-0337) is available on the Health Canada website at the following address: https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt_formats/pdf/compli-conform/info-prod/don/frm-0337-eng.pdf

Note: Although this form is recommended, other formats are accepted as long as all required info is included

Completed FRM-0337 forms are sent to Health Canada at:

Email (preferred method) : hc.bpcp-pcpb.sc@canada.ca
Fax: 1-613-960-2156

E/A Annual Report

section 108

Have SOPs!

- All E/A investigations in previous 12 months
  - E/As related to regulated activities
  - E/As identified **before and after** blood distribution
  - Probability **or not** of the E/A causing a serious adverse reaction
- Include a critical and concise analysis of investigations indicating any trends or recurring issues

If previously unidentified E/As that should have been reported to HC are discovered while the report is being prepared, Health Canada must immediately be notified

Annual reports are generally verified during inspections but may be requested by Health Canada at any time

E/A Examples

- A nurse notices that the Rad-Sure indicator on a unit of irradiated red blood cells is not the right colour. The nurse contacts the blood bank and sends the unit back. It is confirmed that the unit was in fact not irradiated even though it was labelled as such.
  ERROR TO BE REPORTED TO BPCP (because blood was distributed, even if not transfused)

- At a blood bank, a unit of red blood cells was left outside the storage refrigerator for 120 minutes. The blood bank's policy (based on the CSA standard) states that red blood cells may be left outside a temperature-controlled environment for a maximum of 60 minutes. The unit was then distributed without the temperature of the blood being checked beforehand.
  ERROR TO BE REPORTED TO BPCP

E/A Examples continued

- The blood bank is informed by the device manufacturer that the blood bags from lot number 1234 used during pooling had a manufacturing defect (pinholes not visible to the naked eye) that could compromise the safety of the blood. Upon investigation, the blood bank learned that three units of the implicated blood were transfused. **ACCIDENT TO BE REPORTED TO BPCP**

- Cold packs used for the transport of red blood cells by hospital A were stored at a temperature below the required standard. The packed cells arrived at Hospital B below the acceptable temperature and were deemed unsafe for transfusion because they were frozen and haemolysed.
  ERROR TO BE REPORTED TO BPCP

- An operating room employee, who returns non-transfused blood to the blood bank at the end of each day, notices that two units of red blood cells had been in the OR for three days with no record of where they were stored. These units were returned to the bank, placed in inventory, then immediately redistributed. **ERROR TO BE REPORTED TO BPCP**

E/A Examples continued

- The blood bank refrigerator malfunctions and the temperature was too high for a full day. The alarm never sounded because it had been deactivated. Units of blood were distributed throughout the day.
  ERROR TO BE REPORTED TO BPCP

- The establishment that collected the blood sends a notice of component recall/withdrawal to a hospital to request that two units of red blood cells be quarantined because the corresponding platelet units tested positive for bacterial growth. Hospital staff retrieves the two units and places them in the quarantine section of the refrigerator. However, they misread one of the unit numbers and quarantined the wrong unit. One of the recalled units is transfused after the hospital had already processed the recall notice. The error is only discovered once the units are returned to the collecting establishment. **ERROR TO BE REPORTED TO BPCP**

E/A Examples continued

- A box of red blood cells was distributed from site A to site B. Upon receiving the blood, site B notices that the packaging is compliant but that the tamper-proof seal is missing.
  ERROR NOT REPORTABLE As per section 103, site B must report the incident to site A because shipping is a regulated activity (sections 75–76) and blood safety could have been compromised. Site A is not required to report to Health Canada because it is unlikely that the incident could have resulted in a serious adverse reaction if the blood was to be transfused. However, site A must investigate to determine why the seal was absent and if any measures are required (e.g., retraining the employee at fault and/or relocating the seals to facilitate their use during packaging).

- A unit of plasma is distributed using the pneumatic tube system to the intensive care unit at 6 a.m. At 6:30 a.m., the ward calls the blood bank to tell them that the plasma is yet to arrive. After following up, the blood bank realizes that the plasma was sent to the wrong ward.
  NOT AN ERROR UNDER THE BLOOD REGULATIONS (order preparation)
  However, investigation and reporting may be necessary according to provincial or hospital requirements

Adverse Reactions
Investigation and Reporting to Health Canada

Sections 109–116

Adverse reactions overview

sections 110 to 116

- All establishments must comply with regulatory requirements for adverse reactions (ARs)

Including unregistered blood banks

- In the event of an adverse reaction, the blood establishment must (as applicable):
  - identify and quarantine the implicated bloo
  - notify
  - investigate
  - report to Health Canada
  - cooperate and communicate

By the investigating establishment only if the AR is unexpected or serious

Definitions under the Blood Regulations

transfusion reaction

Adverse reaction

An undesirable response that is associated with:

a) in the case of a donor, the collection of blood
b) in the case of a recipient, the safety of the transfused blood

Serious adverse reaction

An adverse reaction that results in any of the following consequences for the donor or recipient:

(a) their in-patient hospitalization or its prolongation;
(b) persistent or significant disability or incapacity;
(c) medical or surgical intervention to preclude a persistent or significant disability or incapacity;
(d) a life-threatening condition; or
(e) death

Unexpected adverse reaction

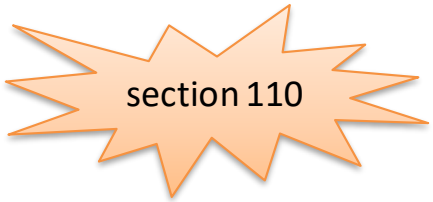
An adverse reaction that is not identified among the possible adverse reactions either in the circular of information or in any other information provided to the recipient.

AR Investigation and notification

- **Adverse <u>Donor</u> Reactions**

At blood collecting establishment during allogeneic or autologous donations

- **Adverse <u>Recipient</u> Reactions (AR)**



An establishment that has **reasonable grounds to believe** that a serious or unexpected AR occurred after the transfusion of blood whose safety was compromised, must immediately take the measures set out in the section.

Section 111 is for autologous donations

The establishment must immediately:
(1) identify the donation codes of the implicated blood
(2) locate and quarantine the implicated blood

section 110

(3) the establishment must conduct a preliminary investigation to determine if the AR is attributable to an activity it carried out that may compromise the safety of the blood

YES

NO

see section 110 for notice contents

The establishment notifies:
(4) the establishment that collected the blood
(5) the establishment from which it received the blood
(6) those to which it distributed the blood

If the information was communicated verbally, a written notice must be sent as soon as possible afterwards

YES

Any establishment that receives a notice:
(7) must perform a preliminary investigation to determine if the AR is attributable to an activity it carried out

No

The establishment must:
(8) conduct an investigation
(9) notify all establishments to which it distributed blood

(10) notify any establishment to which it distributed blood
(11) quarantine the blood
(12) send the investigating establishment any information it has about the blood

AR Investigations - Cooperation and communication

Assisting the investigating establishment – An establishment that transfused or distributed implicated blood must provide all relevant information to the establishment conducting the investigation

section 112

When the root cause of the AR is unclear, the establishment must communicate with the other establishments to share information and help determine the cause (i.e., whether it originates from one of its activities or that of another establishment)

The information is to be provided in a timely manner and includes a list and the final status of the implicated blood

An establishment conducts an INVESTIGATION into a recipient AR

Notify Health Canada of serious or unexpected AR when the safety of the blood is compromised:

- Within 24 hours of a death
- Within 15 calendar days for other serious or unexpected ARs

section 113

Notify any establishment to which it distributed implicated blood:

- Of the investigation results
- Of any measures to be taken, if applicable

section 114

Submit a final report to Health Canada that includes:

- The results of the investigation
- The final disposition of the blood
- Any corrective and preventive measures applied to relevant processes

section 115

Reporting ARs to Health Canada's Canada Vigilance Program

Any form can be used, as long as all requested information is included

PREFERRED METHOD: Web-based secure file transfer. Contact hc.tpmo-bgpc.sc@canada.ca to register and set up an account

By fax:
613-957-0335

AR Annual Report

section 116

- Establishments must prepare, at the end of each year, a report which **summarizes the final reports filed throughout the year** and also provides a concise critical analysis of the investigations that were the subjects of those reports. This annual report must be submitted to Health Canada upon request

Difference with E/A Annual Report
E/A report includes all E/As (reported or not)

Annual AR report includes only reported ARs

It can be the hemovigilance report (but must meet the criteria of section 116)

Examples of serious or unexpected adverse reactions

Serious Adverse Reactions	Unexpected Adverse Reactions
Anaphylaxis	Arrhythmia
Transfusion-related acute lung injury (TRALI)	Loss of consciousness or other neurological deficits
Septicemia caused by a transfusion-transmitted infection (e.g. bacterial, viral, parasitic)	Serious electrolyte imbalance
Graft versus host disease (e.g., ineffective irradiation and improper labelling)	Hypoglycemia and chest pain linked to prolonged transfusion
Serious hemolytic reaction (e.g., incorrect typing or labelling)	
Hypotensive reaction requiring intervention and hospitalization	

REMEMBER – Potential E/A and AR links

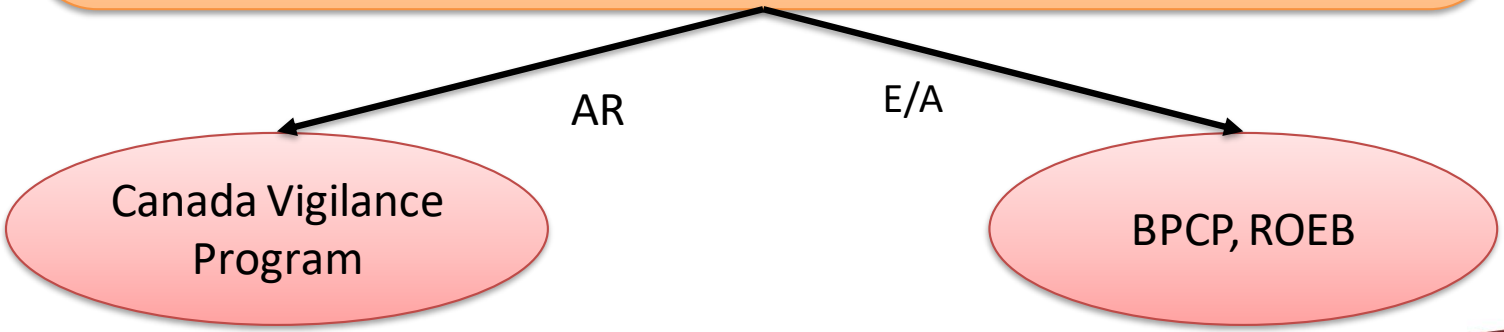
An E/A can cause a serious AR in a recipient. In such cases, the establishment that carried out the regulated activity involving the implicated blood must conduct an investigation and report this AR to the Canada Vigilance Program of the HPFB and also prepare an investigation report for the E/A and report it to the BPCP of the ROEB.

For example, you need to report to the two programs when:

- A serious AR was caused by a contamination that occurred during the washing of a red blood cell unit in an open system with soiled gloves

or

- A serious hemolytic reaction was caused by an E/A during the storage (e.g., refrigerator temperature out of specifications)



AR Examples

- Hospital A is notified by hospital B of a serious hemolytic reaction. The investigation shows that the RBC units were shipped to hospital B by taxi, at night, in winter. Although hospital A was using the same packaging configuration as the collecting establishment, their ice packs and container were different and they had not validated this packaging. Upon receipt of the blood, hospital B notified hospital A that some segments from the empty bags were haemolysed. It was suspected that the units had frozen during transportation.

  AR to be reported to the Canada Vigilance Program by hospital A and also 2 errors to be reported to BPCP by hospital A (inappropriate transport container) and hospital B (inadequate visual inspection on receipt)

- The blood bank was notified of a serious hemolytic reaction that caused the death of the recipient. The recipient, who was O positive, received O-negative blood units in the emergency. No cross-match was done prior to the transfusion owing to the emergency situation. Subsequent testing showed that one of the units received was A-negative rather than O-negative. The blood bank immediately conducted a preliminary investigation and confirmed that no E/A had occurred in its establishment and that the procedures were followed.

  AR to be reported to the Canada Vigilance Program by the collecting establishment (within 24 hours because of the death) and E/A to be reported to BPCP (labelling error) by the collecting establishment as well

AR Examples continued

- A recipient was given two units of red blood cells. One week later, the recipient returned showing signs and symptoms of a delayed serious hemolytic transfusion reaction. The recipient had a history of Anti-Jka antibodies. The two units received from the collecting establishment were labelled as being Jka negative. The recipient was hospitalized and received further transfusions. The blood bank immediately notified the collecting establishment.

  Error and AR to be reported by the collecting establishment. Following their investigation, the phenotyping of an empty blood bag showed that the blood was Jka-positive.

- The blood bank was notified of an immediate serious hemolytic reaction. The investigation showed that even though the information about the recipient on the label was correct, the pre-transfusion sample was collected from the wrong patient with a different blood type. The blood bank had followed all applicable procedures. The AR was caused by the mix-up during the collection of the blood sample for cross-matching.

  Error and AR NOT COVERED by the *Blood Regulations* because it is related to the transfusion practice rather than the safety of the blood (therefore not to be reported nor included in the annual reports)

IMPORTANT

Most of the time, AR reporting to Health Canada is the responsibility of the collecting establishment. However, the blood bank should automatically ask themselves whether one of their activities could be implicated in the AR by means of a preliminary investigation.

It is important to give the investigating establishment all information promptly so they can investigate and answer questions from Canada Vigilance

Other examples

- During preventive maintenance on a platelet agitator/incubator, the alarm was deactivated but not reactivated once maintenance was complete. It was not connected to a central alarm system. During the night, one unit was distributed and transfused. The next morning, an employee checking temperature logs for the previous day noticed that the temperature reading for this device was 26°C (limits are 20 to 24°C). All the platelets were immediately quarantined. An investigation was conducted to determine the cause. Following the investigation, they found that the preventive maintenance procedure on the platelet agitator/incubator did not include instructions to verify that the alarm was reactivated following maintenance. Moreover, the procedure for selecting platelets during transfusion said to check the incubator temperature and the temperature chart. The employee in question said he did not check the temperature before removing the platelets from the device. The recipient experienced no adverse reactions.
  Errors (2) to be reported to BPCP, but no AR to report to Canada Vigilance

- Five units of cryoprecipitates were thawed and immediately placed in the refrigerator for two hours, then pooled, distributed and transfused. The collecting establishment's circular of information says that thawed cryoprecipitates are to be stored between 20 and 24°C. The recipient did not experience any AR.
  Error to be reported to BPCP, but no AR to be reported to Canada Vigilance

Questions?

Biological Product Compliance Program
(Compliance and Enforcement including E/A reporting)
hc.bpcp-pcpb.sc@canada.ca

Canada Vigilance Program (AR reporting)
hc.canada.vigilance.sc@canada.ca

Biologic and Radiopharmaceutical Drugs Directorate (Regulations)
hc.brddopic-bpcidmbr.sc@canada.ca