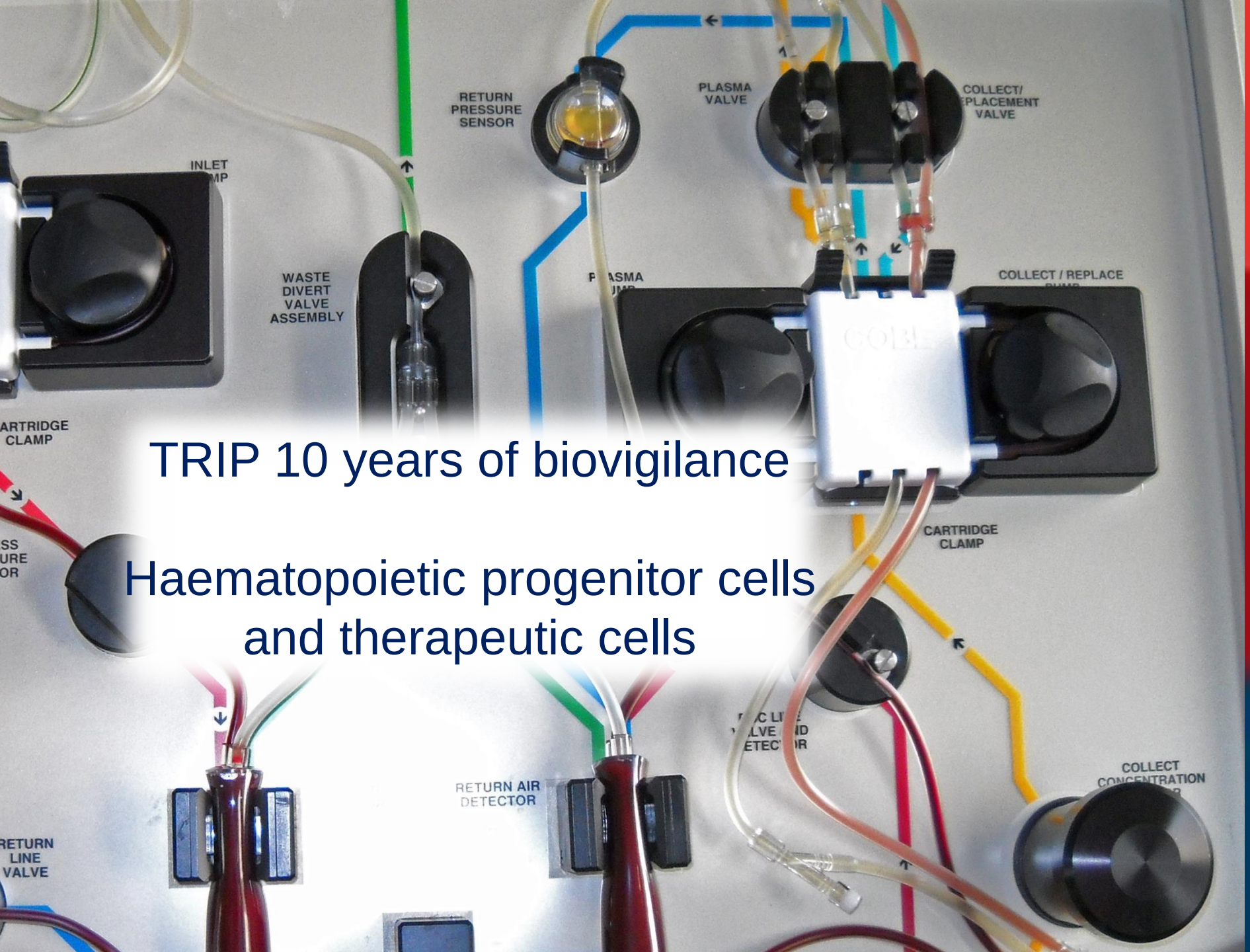


TRIP 10 years of biovigilance

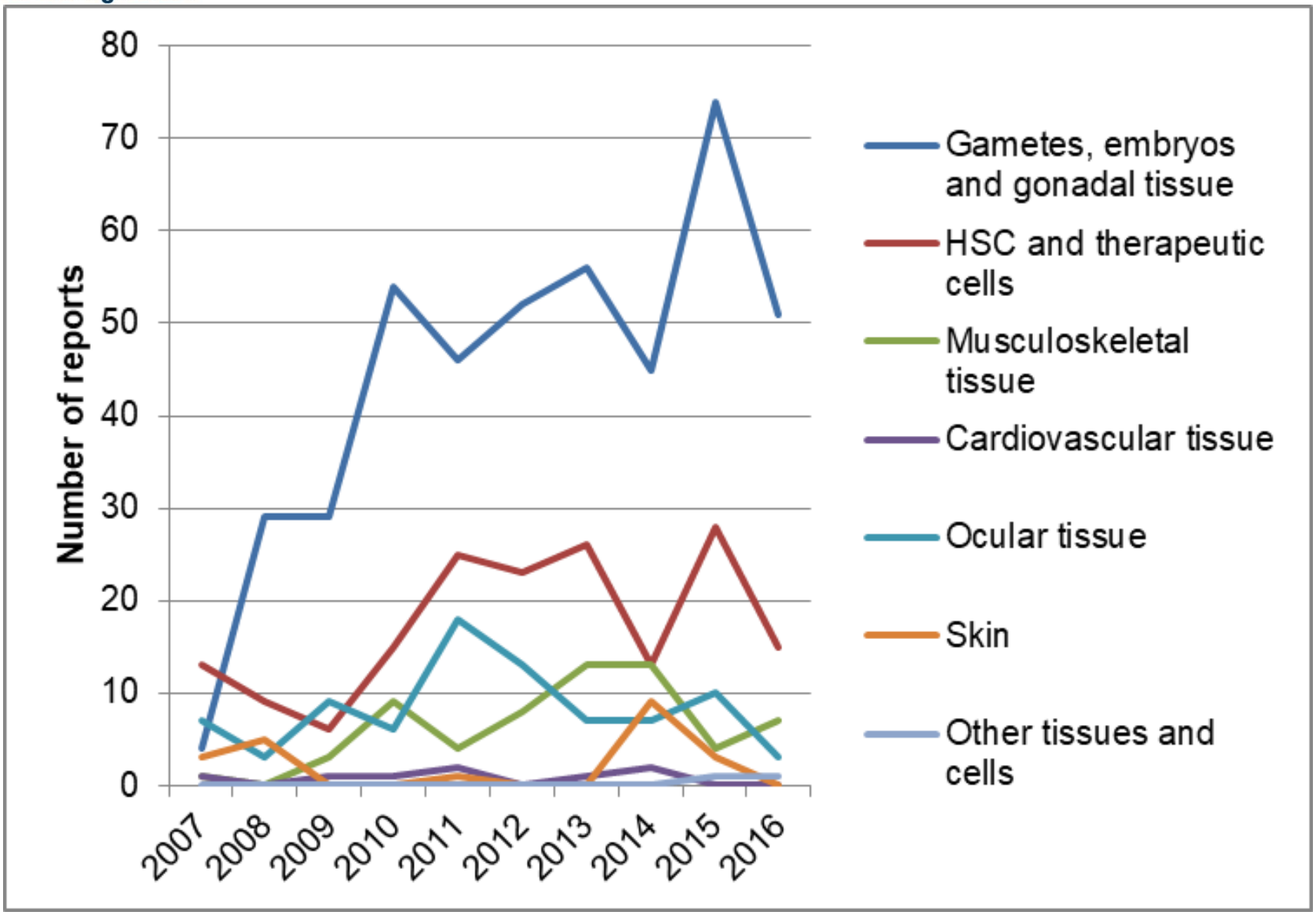
Haematopoietic progenitor cells and therapeutic cells

TRIP
Hemo- en biovigilantie

- TRIP HPC overview 2007-2016
- Case discussions
  - Cross-border travel/transport
  - Leaks and tears in bags
  - Product quality
  - (Recipient) adverse reaction
  - Donation complication
- Discussion

TRIP
Hemo- en biovigilantie

Reports per tissue/cell type per year, 2007-2016



Reactions
incidence estimate

Hemo- en biovigilantie

Tabel 51. Serious adverse reactions in relation to distribution data, transplantations or treatment cycles, 2010- 2014

Tissue or cell type	Serious adverse reaction rate estimation	Per 1000
Gametes, embryos or gonadal tissue	0.01	IUI/donor insemination cycles
Hematopoietic stem cells	2.0	Unrelated stem cell transplants*
	1.0	Related stem cell transplants*
	0.4	Autologous stem cell transplants**
Bone and other musculoskeletal tissues	0.2	Distributed femoral heads
	9.6	Distributed autologous cranial bone flaps
	0.5	Distributed tendons

* *Bone marrow, peripheral blood stem cells and cord blood*

** *Bone marrow and peripheral blood stem cells*

	SAR/1000
Reproductive EU 2014	0.1
Non-reproductive EU 2014	0.3

Adverse events
incidence estimate

Hemo- en biovigilantie

Table 50. Serious adverse events in relation to numbers of tissues/cells processed, transplanted or per treatment cycle, 2010-2014

Tissue or cell type	Serious adverse event rate estimation	Per 1000
Gametes, embryos or gonadal tissue	1.1	IVF/ICSI cycles with follicle biopsy
	0.02	IUI/KID cycles
Hematopoietic stem cells	3.0	Unrelated stem cell transplants*
	1.0	Related stem cell transplants*
	1.2	Autologous stem cell transplants**
Bone and other musculoskeletal tissues	0.2	Processed femoral heads
	1.4	Processed autologous cranial bone flaps
Ocular tissue		
Cardiovascular tissues		

* *Bone marrow, peripheral blood stem cells a*

** *Bone marrow, peripheral blood stem cells*

Serious adverse event (EU)

"any untoward occurrence associated with the procurement, testing, processing, storage and distribution of tissues and cells that might lead to the transmission of a communicable disease, to death or life-threatening, disabling or incapacitating conditions for patients or which might result in, or prolong, hospitalisation or morbidity"

HPC Key findings and recommendations

2006-2011 Stimulate reporting; what is scope? mandatory reporting by tissue establishment (if product-related)

2012 Leaks in bags and collection sets; Stem Cell Laboratory working group will investigate

2013 transportation storage conditions for importation/exportation

2014 donation complications after PBSC donation: later diagnoses of auto-immune/malignant disease

2015 short term complications of G-CSF mobilisation/ PBSC collection

TRIP
Hemo- en biovigilantie

Reports in 2016	Total	Non-serious	Serious
Gametes, embryos & gonadal tissue	52	26	26
Hematopoietic progenitor cells and therapeutic cells	**15**	**13**	**2**
Bone and other musculoskeletal tissue	7	7	0
Skin	0	0	0
Ocular tissue	3	2	1
Cardiovascular tissue	0	0	0
Other tissues and cells	1	1	0
Total	78	49	29

2016 HPC key findings and recommendations

- Fewer reports of donation complications
- Adverse event: modification of the **connector** for anticoagulant solution led to a report of clotting in HPC-A product
- General recommendation: Following an adverse event (e.g. with cord blood, bone, cornea) the **clinical outcome or other consequences** for the patient should be included in the report to the tissue establishment. Lack of this information hinders the vigilance monitoring of adverse reactions and adverse events under the Law on Quality and Safety of substances of human origin.

Cross-border travel

- WMDA: 50% of HPC donations cross international borders

Type	Trans-plantation centres	Recipients	Transplanted units (bags)			
			From NL	From EU	From outside EU	Total
HPC unrelated						
Bone marrow	3	30	1	25	4	30
PBSC	7	308	15	258	37	310
Cord blood	7	69	4	61	31	69
HPC related						
Bone marrow	7	39	38	1	0	39
PBSC	7	123	131	0	0	131
Cord blood	0	0	0	0	0	0
HPC autologous						
Bone marrow	3	4	8	0	0	8
PBSC	12	986	3425	0	0	3425
Cord blood	0	0	0	0	0	0

- PRODUCTS Criteria and tests vary; problems with transportation
- DONOR Can travel (after clearance)

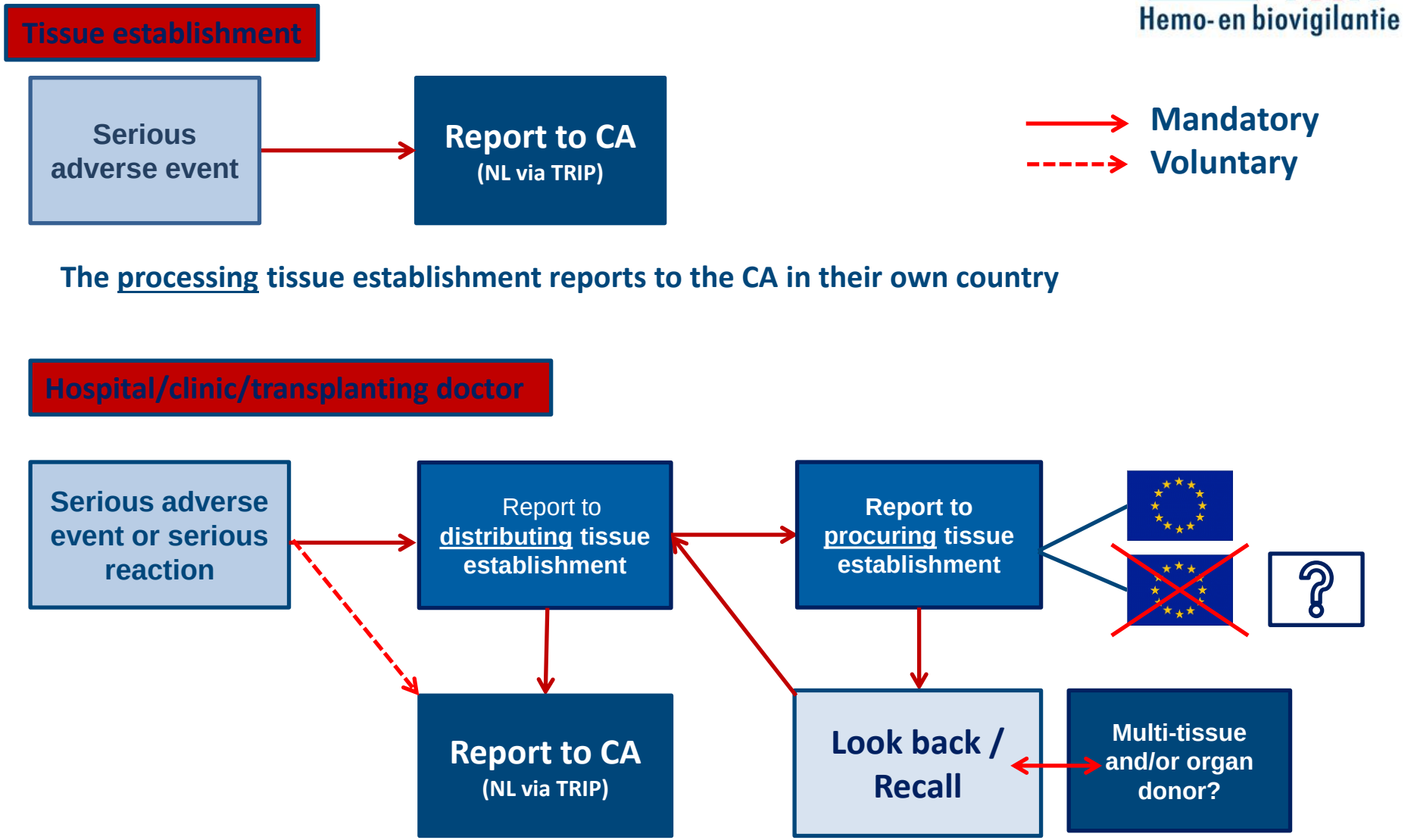
Cross-border HPC reports

- (NL) Cord blood unit thawed on arrival at Transplantation Centre abroad
- (NL) PBSC unit sent abroad: dry ice used in transportation box, product unusable
- Cord blood from abroad: pos bacterial culture (found 1 day after infusion), patient received prophylactic antibiotics
- PBSC unit from abroad: received with spike in port (bacterial culturing at TC negative.)

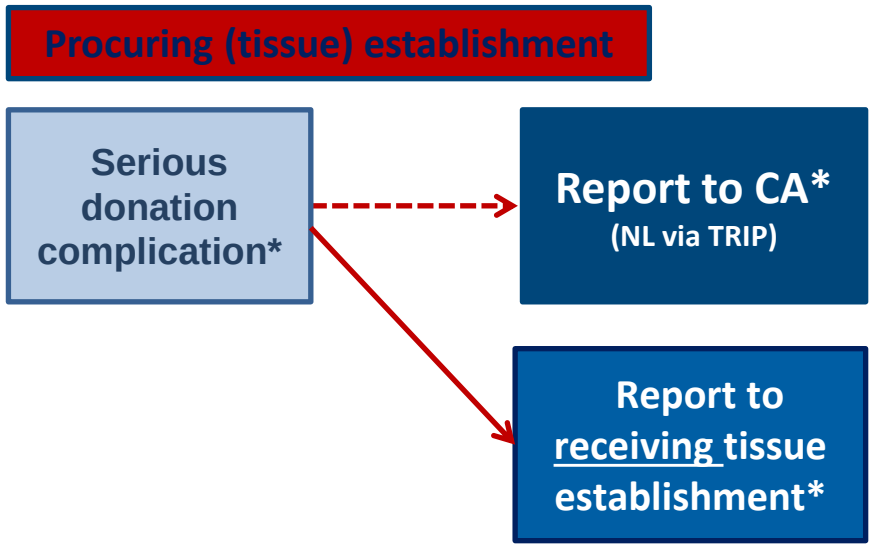
Challenges of cross-border travel of products and donors

- The trace from the donor to the recipient and vice versa may consist of different organisations in different countries. Only tissue establishments are required to report by EU;
- Expertise is required to be able to recognize SEAR/SPEARs and to provide the relevant details in a timely and efficient matter;
- WMDA has set up a robust system for biovigilance of unrelated donors; the related donors are not “yet” part of this system;
- Data protection rules challenge traceability

EU reporting to the competent authority



EU reporting to the competent authority

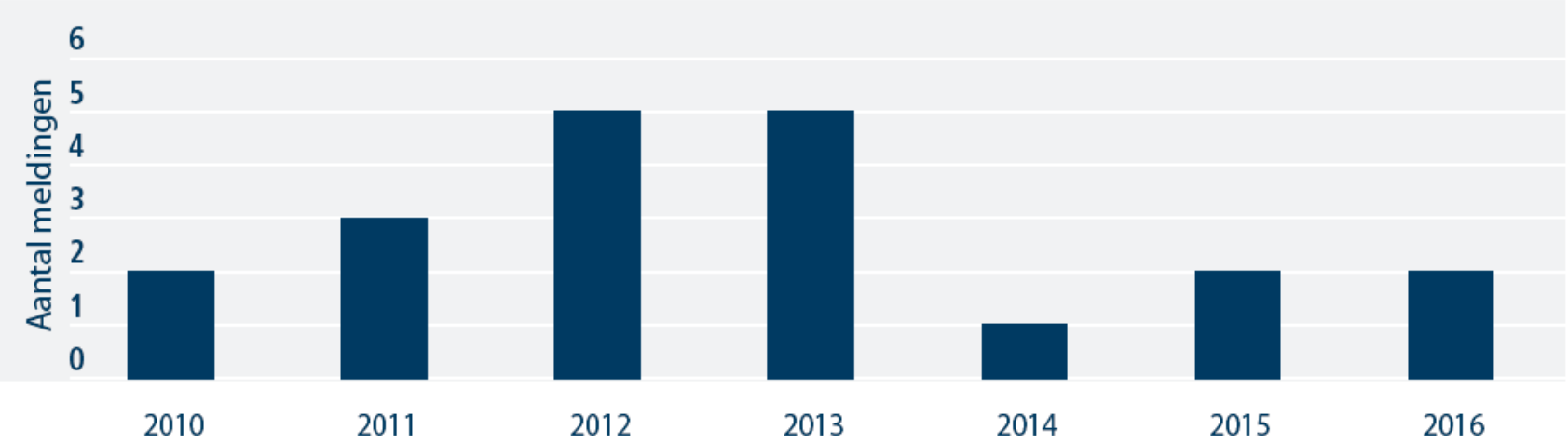


→ Mandatory
** if there is a relation to quality /safety of product or product not available

⇢ Voluntary
*no relation to quality/ safety of product

The procuring tissue establishment reports voluntarily to the CA in their own country; informs the receiving tissue establishment if there is a problem with the product

Reports of leaky/torn HPC bags



Figuur 17. Meldingen van lekkend opvang- en opslagmateriaal van hematopoëtische stamcellen in de periode 2010-2016

2016:
1x Cord blood (bag frozen with too much air)
1x PBSC bag dropped in frozen state; was usable (sterile outer bag)

Bacterial problems (HPC)

2008-2016 Total 25 bacterial contamination	Phase: procurement or processing	Patient consequences?
Bone marrow	7	No adverse reactions
PBSC	12	
Cord blood	3	

Comment: patients often receive prophylactic antibiotics

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DIRECTORATE GENERAL FOR HEALTH AND FOOD SAFETY

Directorate B - Health systems, medical products and innovation
B4 – Medical products: quality, safety and innovation

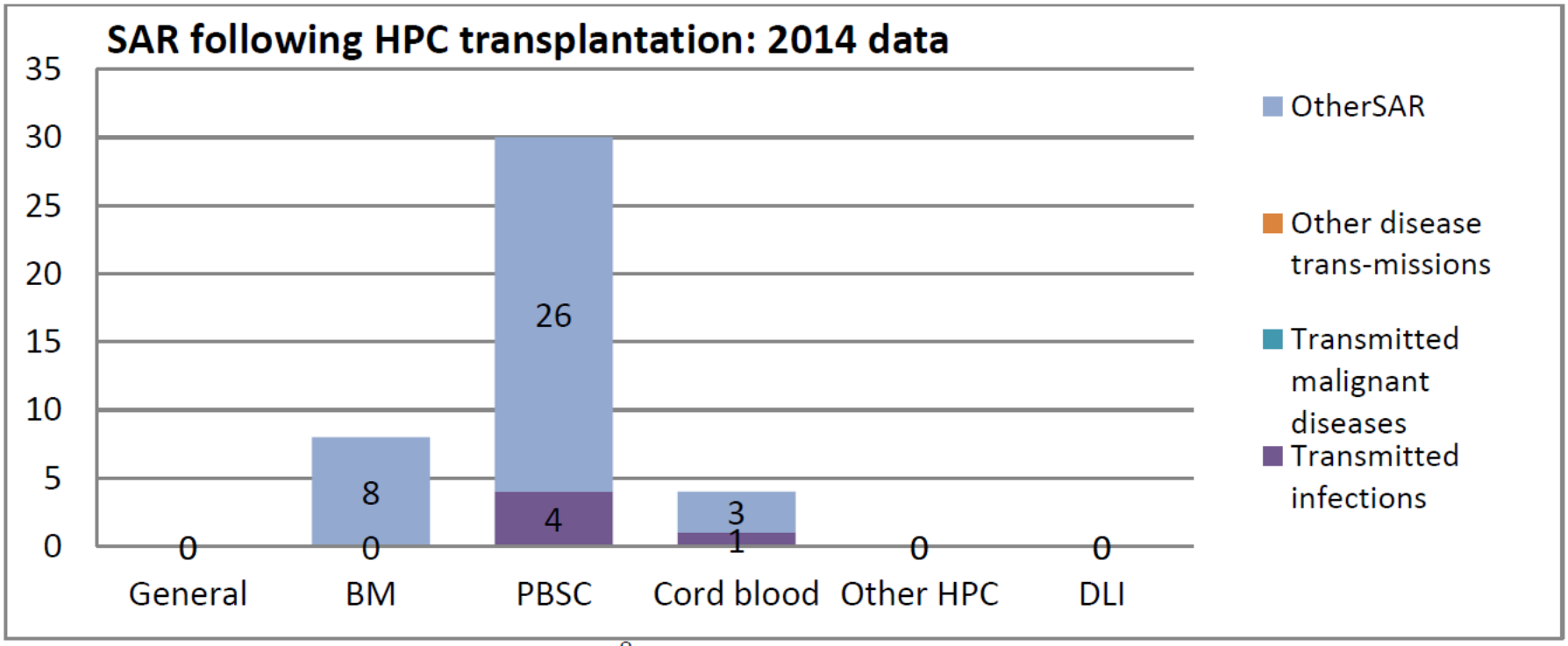

Figure 8. SAR subsequent to HPC[8] transplantation – 2014 data (Total 42 SAR).

Adverse reaction (donation complication)

- Male patient (age 40-50 years) with primary CNS lymphoma
- Developed cough and hemoptysis during HPC-A collection
- CT: segmental pulmonary embolism, admitted for anticoagulation

TRIP report:

Questions -
Was it a smooth procedure? Hematology parameters, was a central venous catheter needed?
Imputability? (patient's illness vs G-CSF?)

Donation complication, severity grade 2, imputability possible

Donation complications, 2007-2016

High imputability donation complications e.g.:

- thrombosis associated with central venous catheter
- splenic rupture (autologous donation)
- Haematuria associated with recurrence of IgA nephropathy during G-CSF
- Hypocalcaemia->termination of apheresis procedure

Later diagnoses e.g.

- Inflammatory bowel disease after 6m
- Breast cancer after 2 years

Is there a product quality/safety link?
Procedural complications
G-CSF --- pharmacovigilance!
Why collect information about later diagnoses?

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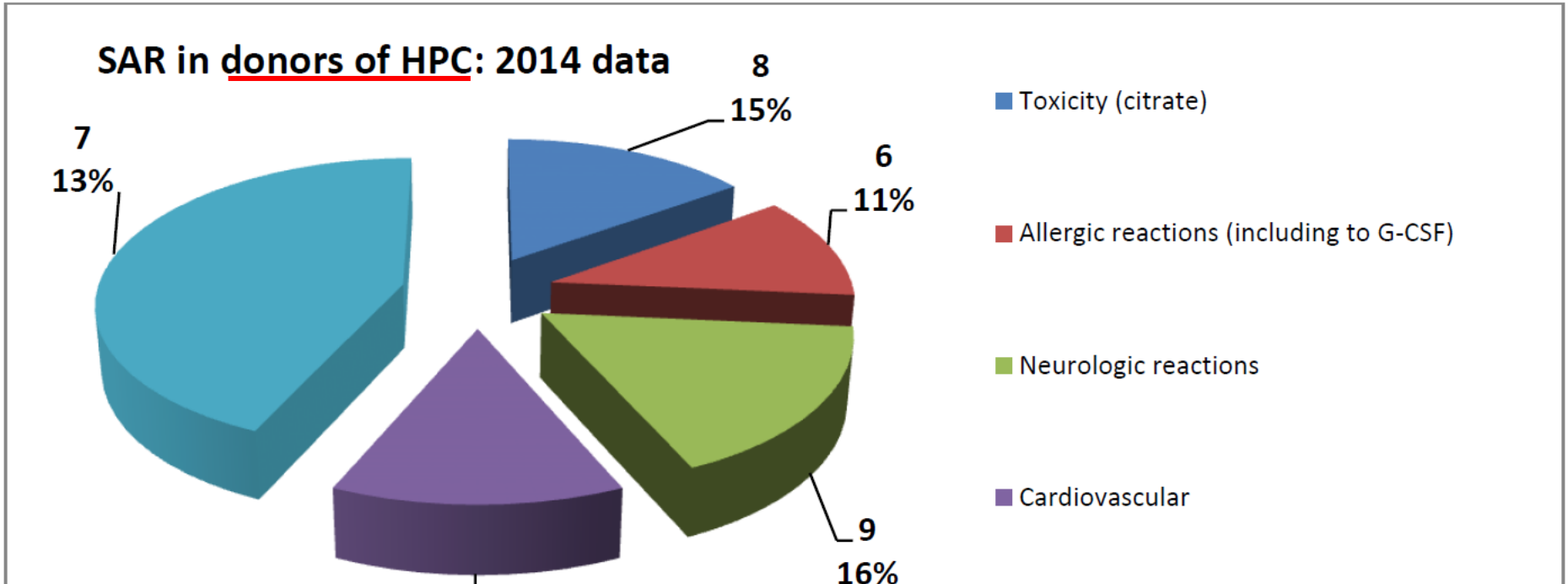
Directorate B - Health systems, medical products and innovation
B4 – Medical products: quality, safety and innovation

Questionnaire to 28 member states +2	Countries (2014)	Total
Reported on donor SAR (non-reproductive)	12	55 SAR
Reported on donor SAR (reproductive)	15	565 SAR



Biovigilance isn't

- Receiving reports (for the sake of it)
- Reiterating (known) side effects
- Pharmacovigilance

10 years of Biovigilance

- Legal requirement
- Learning from each other
- For safety improve-ment

What are the needs of professional groups?

(e.g. monitoring safety of G-CSF)

Nothing reported ≠ everything perfect

10 years of Biovigilance

Thank you!

Mirjam Fechter, Lydia Foeken, Ellen Kramer

Tissue establishment contact persons

Hospital contact persons

Biovigilance professionals in NL and abroad

Ministry of Health, Healthcare Inspectorate, SANTE and others