Regulatory frameworks: HSCT and other cell and tissue therapies

Srinivasan N KELLATHUR, PhD

Pharmaceuticals and Biologics Branch
Pre-market Division
Health Products Regulation Group
Health Sciences Authority

WBMT Graft Processing Workshop
Nov 10-11 2011, Hanoi

Outline

- Overview of Haematopoietic stem cell transplantation (HSCT)
- Worldwide Regulation of Cell and Tissue Therapy, including HSCT
- Substance of Human Origin Vigilance and Surveillance
- Harmonization of Regulation of Cell and Tissue Therapy

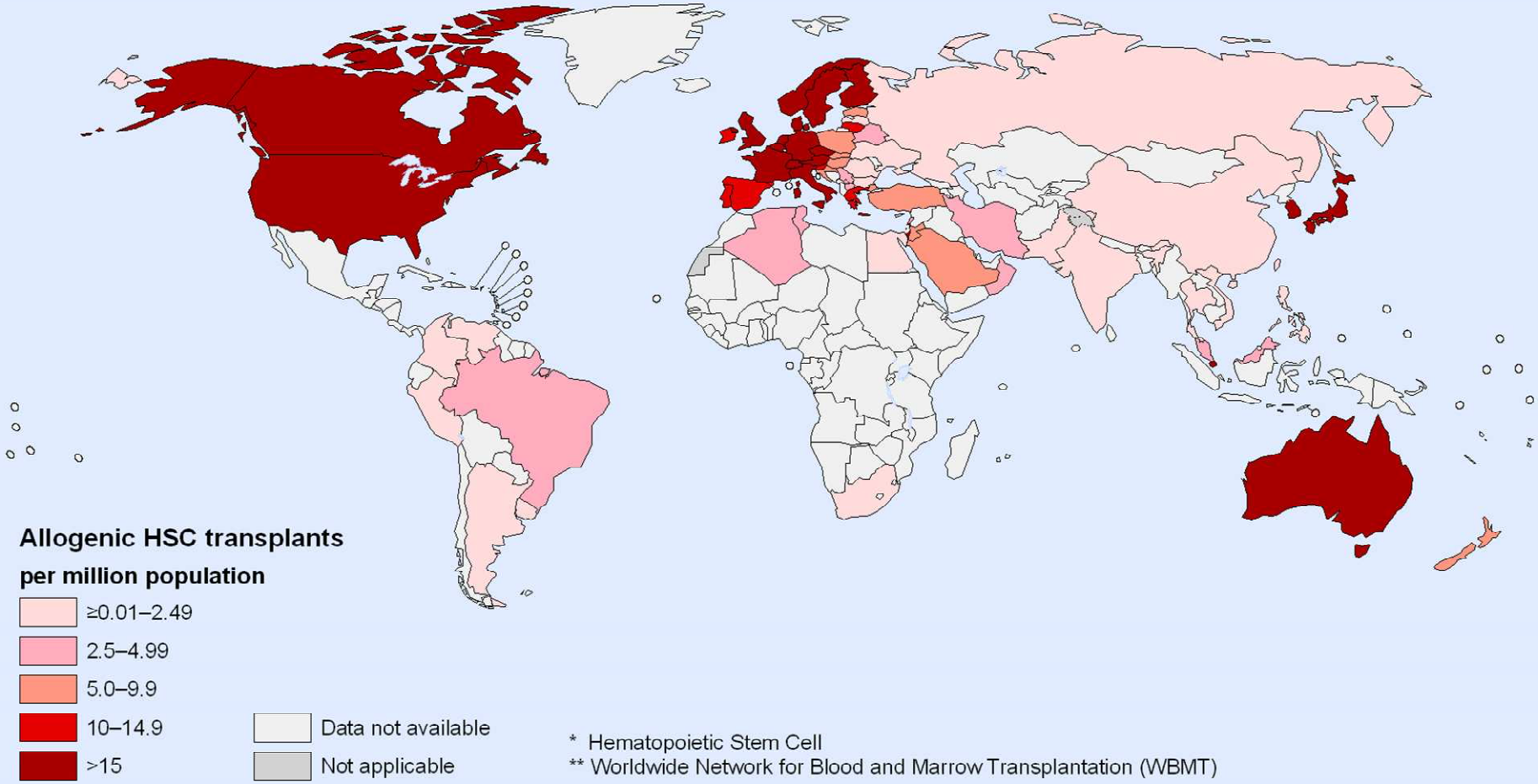
HSCT current status

- Hematopoietic stem cell transplants (HSCT) are now routinely used to treat patients with cancers and other disorders of the blood and immune systems

- HSCT is the transplantation of multipotent hematopoietic stem cells, usually derived from bone marrow, mobilized peripheral blood, or umbilical cord blood that are of either autologous or unrelated allogeneic source

- According to WHO report more than 50,000 transplants are carried out annually worldwide and the number is increasing each year

Allogenic HSC* transplant activities, 2008**



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: Worldwide Network for Blood and Marrow Transplantation (WBMT). Map Production: Public Health Information and Geographic Information Systems (GIS), World Health Organization.

World Health Organization

HSCT regulation – objective

- In the early 90s, haemopoietic stem cells were usually collected from the bone marrow, however last 15 years has seen considerable increase in the use of mobilized peripheral blood haemopoietic stem cells
- Prevent transmission of diseases
  - donor screening and testing
  - process controls to prevent contamination
- Identification (labelling) and traceability

HSCT regulation – objective

- Degree of regulation vary with –
  - degree of manipulation
  - intended use whether for homologous or non-homologous
  - when the peripheral blood stem cells are used as source materials for further manufacture to a cell or gene therapy products
- Good tissue practice standards
  - donor screening, donor testing, donor suitability assessment;
  - retrieval;
  - testing and measurements performed on the cells, tissues or organs after they are retrieved;
  - reparation for use in transplantation;
  - preservation;
  - quarantine;
  - banking or storage; and
  - packaging, labelling and distribution/transport

Cell and tissue therapy Regulations – Global Status

United States

- Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) regulated by US Food & Drug Administration
- HCT/Ps that meet ALL of the following criteria = “361” products
  - Minimally manipulated
  - Intended for homologous use
  - Not combined with drug or device
  - No systemic effect or not dependent on metabolic activity for primary function
  - ❖ No pre-market approval
  - ❖ Comply with Tissue Rules, including tissue establishment registration
- Other HCT/Ps = “351” products
  - Comply with Tissue Rules
  - Regulated as biologics or device (IND/BLA, IDE/PMA/510K)

United States

- Minimally manipulated bone marrow for homologous use i.e. conventional bone marrow transplant falls under the purview of the Health Resources and Services Administration
  - section 379 of the PHS Act
- Other forms of hematopoietic stem cells (from peripheral blood and cord blood, minimally or more-than minimally manipulated), donor lymphocytes (leukocytes) for infusion (DLI), are regulated by US FDA
  - Sections 351 or 361 of the PHS Act
  - Relevant sections of Food, Drug and Cosmetics Act

United States

- The peripheral blood stem cells are by nature blood and blood components
- In many cases, this material may be collected by establishments that also collect blood or other components for transfusion
- These facilities are required to comply with -
  - cGMPs for Finished Pharmaceuticals (21 CFR part 211),
  - cGMPs for Blood and Blood Components (21 CFR part 606),
  - the General Biologic Product Standards (21 CFR parts 600 and 610), and
  - the Additional Standards for Human Blood and Blood Products (21 CFR part 640)
- Same provisions apply to peripheral blood stem cell (PBSCs) products intended for transplantation
- However, manipulated PBSCs and minimally manipulated allogeneic hematopoietic progenitor cells, from cord are evaluated for safety and efficacy under IND and be subject to licensure

Canada

- Health Canada regulates CTT as
  - Drugs
    - Cell therapies in which the safety, efficacy and quality has already been established
      - Autologous or allogeneic use
      - Non-homologous and/or more than minimally manipulated
  - Human cells, tissues and organ (CTO) regulations
    - Cell therapies in which the safety, efficacy and quality has already been established
      - Allogeneic use
      - Homologous use
      - Minimally manipulated
    - Lymphohematopoietic cells that are derived from bone marrow, peripheral blood or cord blood
    - Establishment registration

Europe

- Minimally manipulated cells and tissues
  - Not a medicinal product
  - Regulated under the Tissue Directive (2004/23/EC) - donation, testing, procurement, processing, storage and distribution across EU
  - Tissue establishment authorisation by national drug regulatory authorities
- UK – code of practice for tissue banks applies to tissue banks in the public sector supplying human tissues for therapeutic purposes to the health service
  - The scope of this Code includes all human tissues (including haemopoietic progenitor cells bone marrow, peripheral blood, cord/placental blood) used for therapeutic purposes including those used in clinical trials.

Europe

- Substantially manipulated cells / non-homologous use
  - Advanced therapy medicinal product (ATMP) – medicinal product
    - Somatic cell therapy medicinal product
    - Gene therapy medicinal product
    - Tissue engineered product
  - Comply with tissue regulations
  - Centralised approval procedure by European Medicines Agency (EMA) for marketing authorisation
  - Clinical trial authorisation by national drug regulatory authority

Australia

- Human cells and tissues are regulated under the Biologicals framework by the Therapeutic Goods Administration
  - Biological - comprises, contains or is derived from human cells or tissues
  - Regulation implemented on May 31, 2011
  - Classification based on extend of manipulation and intended use
- The Biologicals framework exclude fresh viable human haematopoietic progenitor cells for direct donor-to-host transplantation for the purpose of haematopoietic reconstitution
  - Haematopoietic progenitor cells or haematopoietic reconstitution are regulated as therapeutic goods but not biologicals and regulated as medicine similar to blood and blood components

Australia

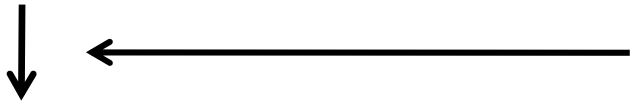
- Class I
  - a biological that is declared in the Regulations as a Class 1 biological
- Class II
  - processed using only one or more of the actions of minimal manipulation; &
  - for homologous use
- Class III
  - processed:
    - using a method in addition to any of the actions of minimal manipulation; &
    - in a way that does not change an inherent biochemical, physiological or immunological property
- Class IV
  - processed:
    - using a method in addition to any of the actions of minimal manipulation; &
    - in a way that changes an inherent biochemical, physiological or immunological property

Singapore

- Proposed regulation jointly developed by MOH-HSA CTT working group
- MOH will regulate the clinical use of CTT product
  - All registered practitioners must get CTT specialised service / special care service license from MOH before administering such products into their patients under the Private Hospitals and Medical Clinics Act (PHMCA)
- HSA will regulate quality, safety and efficacy of high risk CTT product like other biological medicinal products under the Medicines Act

Regulation of Clinical Use of CTT

Application for MOH CTT specialized service license



Product classification by HSA

MOH will review the scientific evidences

MOH CTT Service Licensing T&C applicable to all service licenses

For high risk CTT products (additional controls)

- **GMP compliance**
  - **applicable for processes involving substantial manipulation**
- **Serious ADR reporting and patient registry**

Exempted: Homologous use of minimally manipulated bone marrow intended for transplantation

Risk Classification of CTT

- A CTT product is considered to be of high risk if
  - the CTT product had been subject to substantial manipulation*; or
  - the CTT product is intended for a non-homologous use (i.e. used for a function different from its original function) or
  - the CTT product is combined with a drug, biologic or device.

*processing that alters the original relevant biological, physiological or structural characteristics of cells or tissues, or characteristics of the tissue relating to the tissue's utility for reconstruction, repair or replacement.

Information captured in registry

Patient

- Patient identifier
- Age
- Ethnic group
- Gender
- Indications for the HCT product
- Medical history (including concomitant medications and relevant information

Product

- Product Description
- Brand name (if applicable)
- Batch identifier/number
- Dosing Regimen (Dose, route of administration, Frequency)
- Start date and end date
- Duration of therapy
- Name of cell processing lab

Doctor

- Doctor identifier
- Place of Practice
- Name of company (for clinical trials)
- Name of applicant (for clinical trials)
- Contact of applicant (for clinical trials)

Substances of Human Origin Vigilance and Surveillance (SOHO V&S)

SOHO V&S

- WHO, the Italian National Transplant Centre (CNT) and the EU-funded Project ‘Vigilance and Surveillance of Substances of Human Origin’ (SOHO V&S) joined forces to organise a global initiative aimed at raising the profile of vigilance and surveillance (V&S) of substances of human origin’
- The scope of the project included organs, tissues and cells for transplantation and for assisted reproduction.
- International experts were invited to lead 10 working groups with specific defined tasks
  - Organs, tissues (other than ocular, HPCs, ocular tissues, games and embryos
  - Infection, malignancies, product properties, clinical practice, genetics and donor

SOHO V&S

WHO Guiding Principles on Human Cell, Tissue and Organ Transplantation

1.Consent for deceased donor's donation

2.No conflict for death determination

3.Deceased but also consenting live donors

4.Protection of minors and incompetent persons

5.No sale or purchase

6.Promotion of donation no advertising nor brokering

7.Responsibility on origin of transplant

8.Justifiable professional fees

9.Allocation rules

10.Quality safety efficacy of procedures and transplants

11.Transparency and confidentiality

SOHO V&S

- The project is intended to develop instruments and guidance for tissue and cell V&S in the EU based on the data gathered and the recommendations developed by the Bologna Initiative
- WHO will publish a booklet for clinicians that will summarise the guidance on detection and investigation of adverse reactions and events to promote V&S in transplantation
- Public database – is intended as a communication hub for institutions and organisations worldwide collaborating in the facilitation of access to Vigilance and Surveillance information
- The initiative will facilitate global sharing of V&S information and guidance for the enhancement of donor and recipient safety and for greater public transparency in transplantation and assisted reproduction

Cell Therapy Harmonisation

CTT product – challenges

- Complex and highly innovative manufacturing processes
- Process can impact safety, quality and biological activity of product
- Challenges in product characterization – purity, potency, consistency
- Sometimes custom made for individual patients and each batch manufactured independently of the next

Cell therapy harmonisation

- ICH regulatory forum agreed to form a brainstorming group to consider
  - Potential areas for harmonization
  - Potential approaches (e.g. regulatory dialogue, workshops)
- Strategy agreed upon
  - Step-wise approach
  - Fact-finding to determine the topic for formal harmonization
- ICH steering committee (SC) and working group meeting, Cincinnati, Ohio from June 11-16, 2011
  - Press release: A group of global regulators cooperating in the area of cell therapy updated the ICH SC on their activities and reported that they are exploring potential areas for future harmonization or other approaches to regulatory convergence

Cell therapy harmonisation

- Fact-finding and inventory
  - Understand and distinguish the regulatory landscape in different regions
  - Current existing guidance documents
  - Authorized cell therapy products
  - Clinical trials and others under development
- Survey tool (questionnaire) developed to gather information
- WHO and PAHO are engaged to help facilitate broader reach in info gathering
- APEC LSIF RHSC endorsed workshop on QA/QC of stem cell products

Conclusions

- Internationally cell and tissue therapy regulatory framework is in different states of maturity
- Regulation of cell and tissue therapies in a risk-based approach
  - Manufacturing of the product
  - Intended use of the product
- CTT products broadly fall under the pharmaceutical/medical device regulatory framework with specific technical requirements to this category of products
- Need for harmonizing technical requirements at this initial stage rather than wait for regulatory divergences to occur

THANK YOU

Srinivasan N KELLATHUR, PhD

Senior Regulatory Specialist
Pharmaceuticals and Biologics Branch
Pre-market Division
Health Products Regulation Group
kellathur_srinivasan@hsa.gov.sg

References

- http://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/default.htm
- http://www.fda.gov/BiologicsBloodVaccines/TissueTissueProducts/default.htm
- Canadian National Standard
  - CAN/CSA Z900.1-03: Cells, Tissues, and Organs for Transplantation and Assisted Reproduction: General Requirements
  - CAN/CSA-Z900.2.5-03: Lymphohematopoietic cells for transplantation
- Guidelines for Preventing Opportunistic Infections Among Hematopoietic Stem Cell Transplant Recipients - Recommendations of CDC, the Infectious Disease Society of America, and the American Society of Blood and Marrow Transplantation
- Council of Europe's Safety and quality assurance for the transplantation of organs, tissues and cells
- http://www.hc-sc.gc.ca/dhp-mps/compli-conform/info-prod/cell/index-eng.php
- http://www.tga.gov.au/industry/biologicals.htm
- http://www.who.int/transplantation/en/

Legislation	Date	Source	Title
Resolution (78) 29	1978	EU	On harmonization of legislation of member states relating to removal, grafting and transplantation of human substances.
Recommendation R(94)1	1994	EU	On human tissue banks.
Guidance	2001	UK DH	A *Code of Practice for Tissue Banks* providing tissues of human origin for therapeutic purposes.
Directive 2001/20/EC	2001	EU	On the approximation of the laws, regulations and administrative provisions of the members states relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.
Guidance	2002	CoE	Guide to safety and quality assurance for organs tissue and cells (1st edn).
Directive 2003/83/EC	2003	EU	On the community code relating to medicinal products for human use.
Directive 2003/94/EC	2003	EU	Laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use.
Guidance	2004	CoE	Guide to safety and quality assurance for organs tissue and cells (2nd edn).
Directive 2004/23/EC	2004	EU	On setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells.
Human Tissue Act 2004	2004	E, W & NI	The Human Tissue Act.
Directive 2006/17/EC	2006	EU	Implementing Directive 2004/23/EC of the EP and CoE as regards certain technical requirements for the donation, procurement and testing of human tissues and cells.
Directive 2006/86/EC	2006	EU	Implementing Directive 2004/23/EC of the EP and CoE as regards traceability, requirements, notification of serious adverse reactions and events and certain technical requirements for coding, processing, preservation, storage and distribution of human tissues and cells.
Statutory Instrument 2006 No. 1659	2006	UK	The Human Tissue Act 2004 (Persons who Lack Capacity to Consent and Transplants). Regulations 2006.
Statutory Instrument 2006 No. 1260	2006	UK	The Human Tissue Act 2004 (Ethical Approval, Exceptions from Licensing and Supply of Information about Transplants) Regulations 2006.
HTA Code of Practice	2006	UK	Consent.
HTA Code of Practice	2006	UK	Donation of organs cells and tissue for transplantation.
HTA Code of Practice	2006	UK	Post-mortem examination.
HTA Code of Practice	2006	UK	Anatomical examination.
HTA Code of Practice	2006	UK	The removal storage and disposal of human organs and tissues.
HTA Code of Practice	2006	UK	Donation of allogeneic bone marrow and peripheral blood stem cells for transplantation.

Eu, European Union; UK DH, UK Department of Health; CoE, Council of Europe; E, W & NI, England, Wales & Northern Ireland; EP, European Parliament.

Relevant article	Relevant annex
2006/17/EC	
Article 2 Requirements for the procurement of human tissues and cells	**Annex I** Selection Criteria for donors of tissues and/or cells (except donors reproductive cells) as referred to in Article 3(a) – Section 2. Living donors
Article 3 (a) Selection Criteria for donors of tissues and cells	**Annex II** Laboratory tests required for donors (except donors of reproductive cells) as referred to in Article 4(1) – Section 1. Biological tests required for donors – Section 2. General requirements to be met for determining biological markers
Article 4 Laboratory tests required for donors	
Article 5 Tissue and/or cell donation and procurement procedures and reception at the tissue establishment	**Annex IV** Cell and/or tissue donation and procurement procedures and reception at the tissue establishment as referred to in Article 5 – Section 1. Donation and procurement procedures – Section 2. Reception of the tissue/cells at the tissue establishment
2006/86/EC	
Article 3 Requirements for the acreditation, designation, authorization or licensing of tissue establishments	**Annex I** Requirements for the acreditation, designation, authorization or licensing of tissue establishments as referred to in Article 3 – Section A. Organisation and management – Section B. Personnel – Section C. Equipment and materials – Section D. Facilities/premises – Section E. Documentation and records – Section F. Quality review
Article 4 Requirements for the accreditation, designation, authorisation, licensing of tissue and cell preparation processes.	**Annex II** Requirements for the authorisation of tissue and cell preparation processes at the tissue establishments as referred to in Article 4. – Section A. Reception at the tissue establishment – Section B. Processing – Section C. Storage and release of products – Section D. Distribution and recall. – Section E. Final labelling for distribution. – Section F. External labelling of the shipping container
Article 5 Notification of serious adverse reactions	**Annex III** Notification of serious adverse reactions – Part A. Rapid notification for suspected serious adverse reactions – Part B. Conclusions of serious adverse reactions investigation
Article 6 Notification of serious adverse events	**Annex IV** Notification of serious adverse events – Part A. Rapid notification for suspected serious adverse events – Part B. Conclusions of serious adverse reactions investigation
Article 9 Traceability	**Annex VI** Information on the minimum donor/recipient data set to be kept as required in Article 9 – Section A. By tissue establishments – Section B. By organisations responsible for human application
Article 10 European coding system	**Annex VII** Information contained in the European coding system