Cell Bank Safety Testing for Cellular Therapeutics

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Introduction

Definitions used in this talk

- Cellular therapeutics (CTP)
  - EU: Advanced Therapy Medicinal Products (ATMP)
    - somatic cell therapy medicinal products
    - tissue engineered products (TEP)
    - *[gene therapy medicinal products]*
  - US: Human cell and tissue products (HCT/P)
- Cells and tissues can either be:
  - Transplants – minimally manipulated and used for the same essential function (homologous use)
    - EUTCD (Directive 2004/23/EC) only/GTPs only (21CFR1271)
  - CTP – more than minimally manipulated and/or not used for the same essential function.

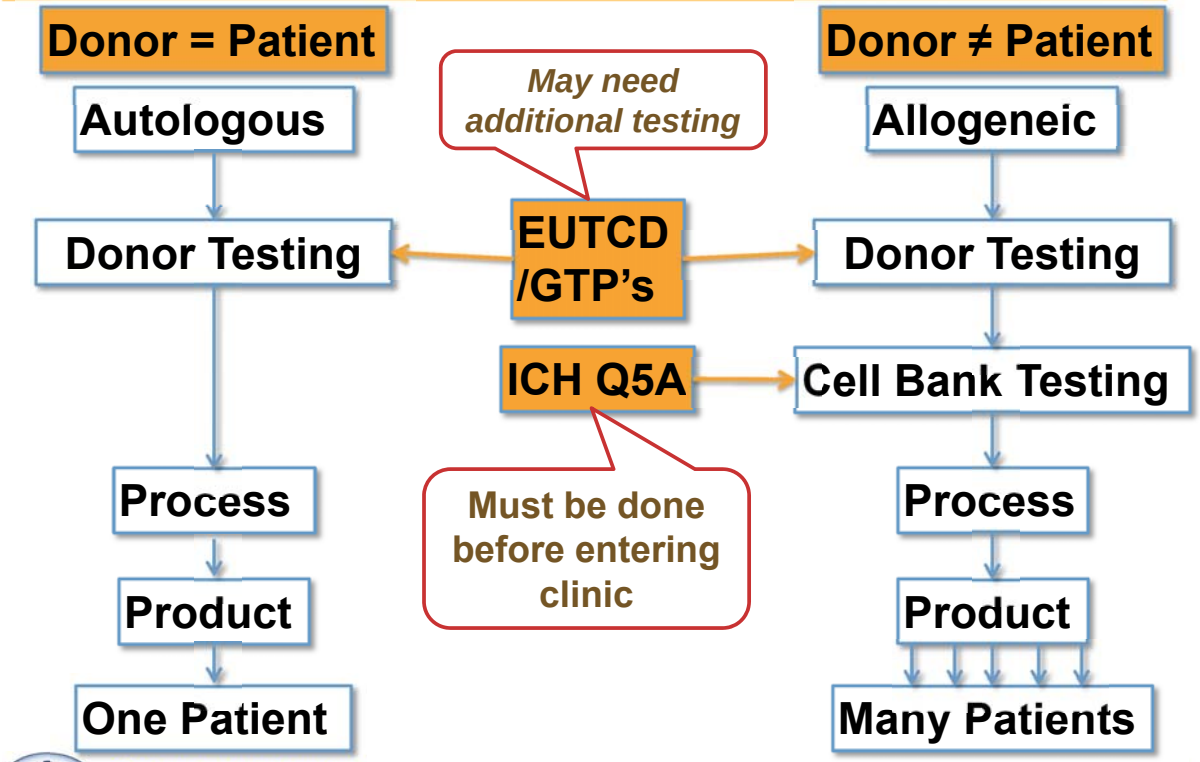
Introduction
Why are CTP different?

- As with other biological medicinal products (biologics), those based on living cells:
  - Cannot be sterilised
- But unlike other biological medicinal products other biological medicinal products
  - Cannot incorporate viral reduction/elimination steps
  - Can harbour and propagate viruses
  - Adventitious agents present in other raw materials could also contaminate the cells and be propagated.
- For these reasons there is a greater need to control adventitious agents at the level of starting and raw materials.

Introduction
Why are CTP different?

- Autologous (donor = patient) do not utilise traditional cell banks
  - although may utilise frozen intermediate (*not discussed*)
- Allogeneic (donor ≠ patient) typically (but not always) utilise a cell bank, however:
  - Cell lines (primary) typically have limited expansion capacity
    - Pluripotent stem cells assumed to be exception (TBD)
  - Batch sizes still tend to be small
    - In some cases a single tier bank is sufficient
  - In many/most cases a single MCB/WCB (one donor) will not be sufficient for the product lifecycle

Starting Material Testing



See also guideline for viral testing of IMPs (not specific to cell products)
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003798.pdf

Donor Testing Requirements

Screening/Testing	FDA	EMA
Testing Requirements HIV 1&2, HBC, HCV, HTLV 1&2 (leukocyte rich cells only) Chlamydia and Gonorrhea (for reproductive cells only	• Test Methods not specified • Syphilis, West Nile Virus	• EMA Methods Specified (Ab vs. Ag) • Member States additional testing
Donor Test Kits	FDA Approved/Cleared	CE Marked/NCA approved
Travel History	Specific regions identified	General Assessment for risk
Medical History	Assess for risk factors	Additional – Specified chronic autoimmune diseases deferral
Responsible Person	No requirements	Minimal requirements
Collection Site	Registered with FDA	Registered Tissue Establishment with Member States
Donor Record Retention	10 years	30 years
Autologous somatic cells	No donor testing requirements	Same as allogeneic somatic cells

FDA Donor Eligibility - TSE Risk

Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products, FDA 2007

LIST OF BSE-AFFECTED COUNTRIES APPLICABLE TO DONOR DEFERRAL

European Countries to be Used for Deferral of Donors Based on Geographic Risk of BSE

Albania, Austria, Belgium, Bosnia-Herzegovina, Bulgaria, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Liechtenstein, Luxembourg, Macedonia, Netherlands, Norway, Poland, Portugal, Romania, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, United Kingdom[1], and Yugoslavia.

[1]For purposes of this guidance, the United Kingdom should include all of the following: England, Northern Ireland, Scotland, Wales, the Isle of Man, the Channel Islands, Gibraltar, and the Falkland Islands.

Donor Testing – General Requirements

Adventitious Agent	Test	Directive 2006/17/EC	Additional National	NCA's	FDA Requirement
HIV 1 and 2	Ag		Yes	CZ, FR, MT, RO	
	Ab	Yes			Yes
	NAT		Yes (HIV-1)	BE[a], DK, EE, IT, HU, PT, SK	Yes (HIV-1)
Hepatitis B	Ag	Yes			Yes
	Ab	Yes			Yes
	NAT		Yes	BE[b], DK, ES, IT, HU, MT, PT	Yes
Hepatitis C	Ag				
	Ab	Yes			Yes
	NAT		Yes	BE[a], DK, DE, ES, IT, HU, MT, PT	Yes
Syphilis		A validated testing algorithm must be applied to exclude the presence of active infection.			Yes
HTLV-1	Ag				
	Ab	Where risk	Yes*	BG, DE, EL, ES, FR, HU, RO	Yes
	NAT				
CMV	Ag				
	Ab	No	Yes (IgG/M)*	HR, FR, IT[c], LT, MT, RO, ES, SE	Yes
	NAT				

[a] or second serology at 6 months
[b] to be implemented
[c] IgG and IgM, for amniotic membrane, skin, heart valves and haematopoeitic progenitor cells
[d] IgM, amniotic membrane
[e] Assumed to be for gametes only (unclear)

Donor Testing – Additional tests

Other NCA testing requirements (unclear whether always required)				
Toxoplasma	Ag			
	Ab		Yes (IgG/M)*	HR, IT[d], LT, RO
	NAT			
N.gonorrhoeae				
	ND		Yes*	DK
EBV	Ag			
	Ab		Yes (IgG)*	LT, RO
	NAT			
Chlamydia	Ag			
	Ab			
	NAT		Yes*	MT[e]

[a] or second serology at 6 months
[b] to be implemented
[c] IgG and IgM, for amniotic membrane, skin, heart valves and haematopoeitic progenitor cells
[d] IgM, amniotic membrane
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Selecting Biological Starting and Raw Materials

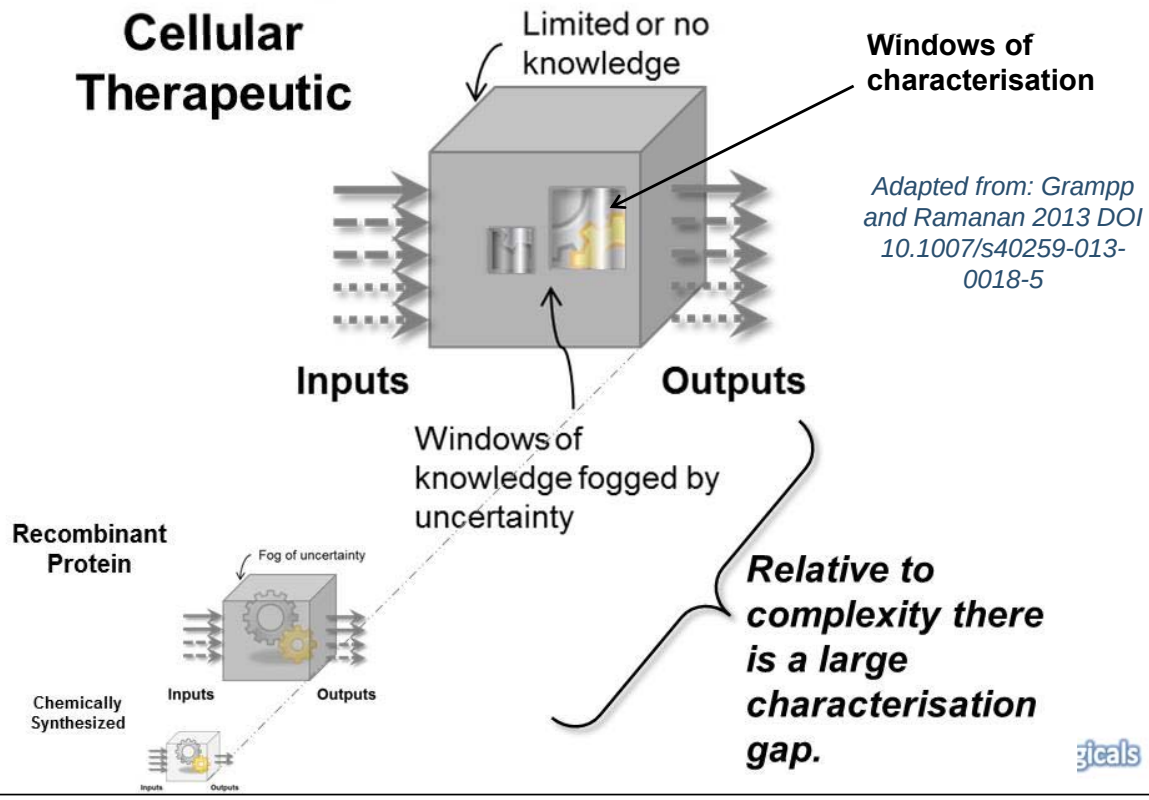
- Materials of biological origin pose significant concerns for safety and performance.
- Biological materials may harbour bacteria and viruses
- Biological function can be (highly) variable between both batches and suppliers, and is usually highly sensitive to storage and handling conditions
- Consequently you are more likely to need to do in-house testing to supplement the suppliers CoA or confirm suitability for your use, e.g. growth characteristics for serum, biological activity

Conclusions

- CTP pose some unique challenges for cell banking
- Both the donor material and other biological raw materials can introduce adventitious agents into the product
- Living cell products can neither be sterilised nor are there viral clearance methods available
- Consequently greater care is needed to ensure the adventitious agent safety of raw materials

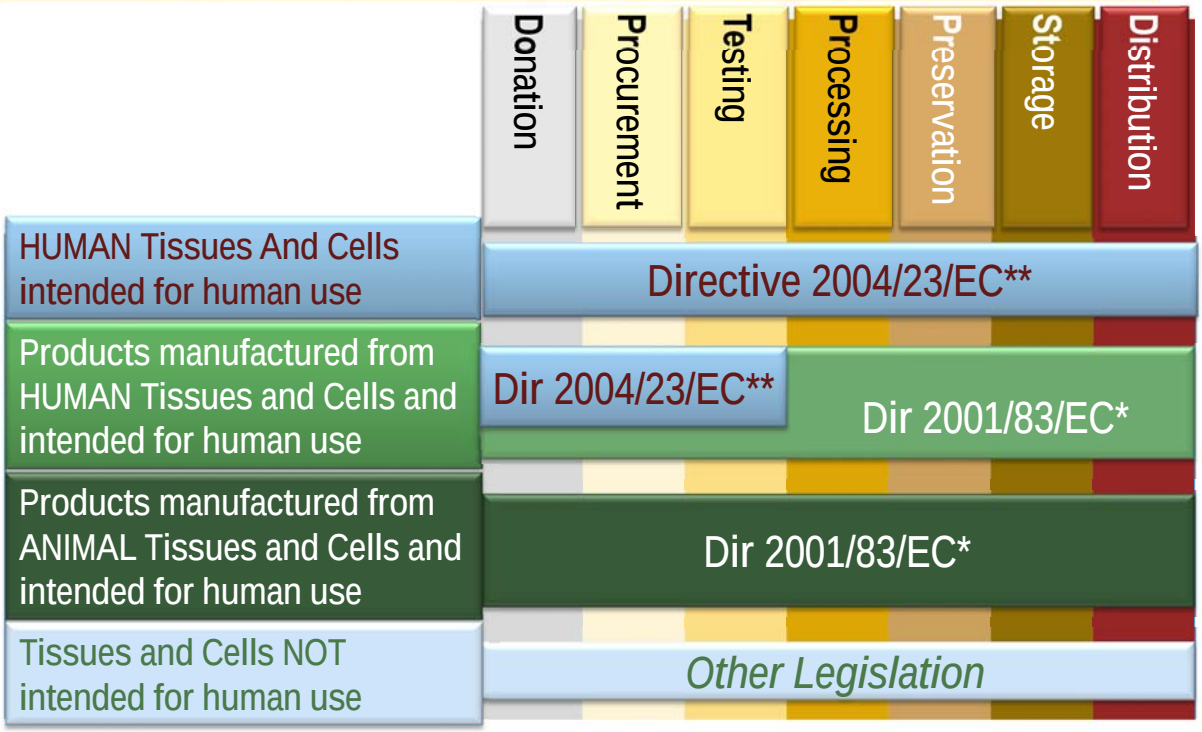
Back-up Slides?

Introduction
Why are CTP different?



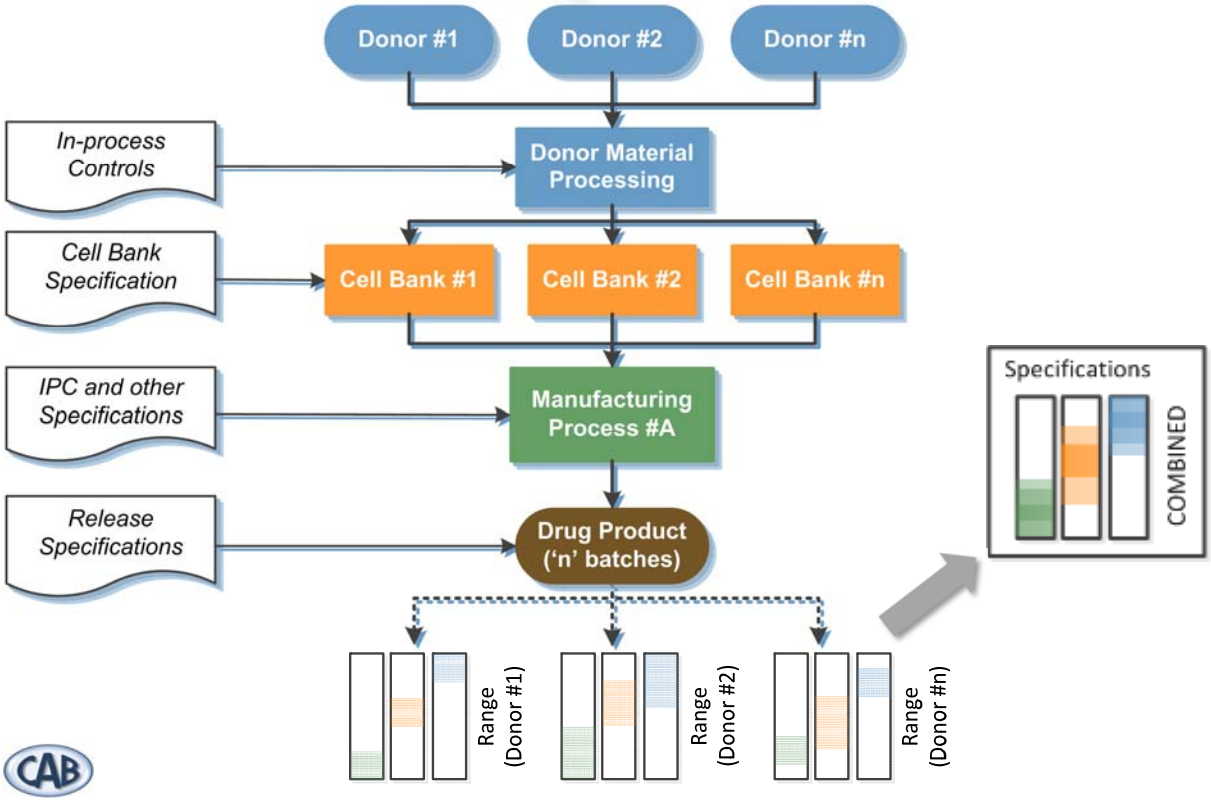
Adapted from: Grampp and Ramanan 2013 DOI 10.1007/s40259-013-0018-5

Regulation of Human and Animal Tissues and Cells for Therapeutic Purposes



*As amended, incl. Reg (EC) No 1394/2007

Multiple MCB required over product life-cycle



Adds complexity to comparability following other process changes