

# Regulatory Guidances, Trends, and Data Quality

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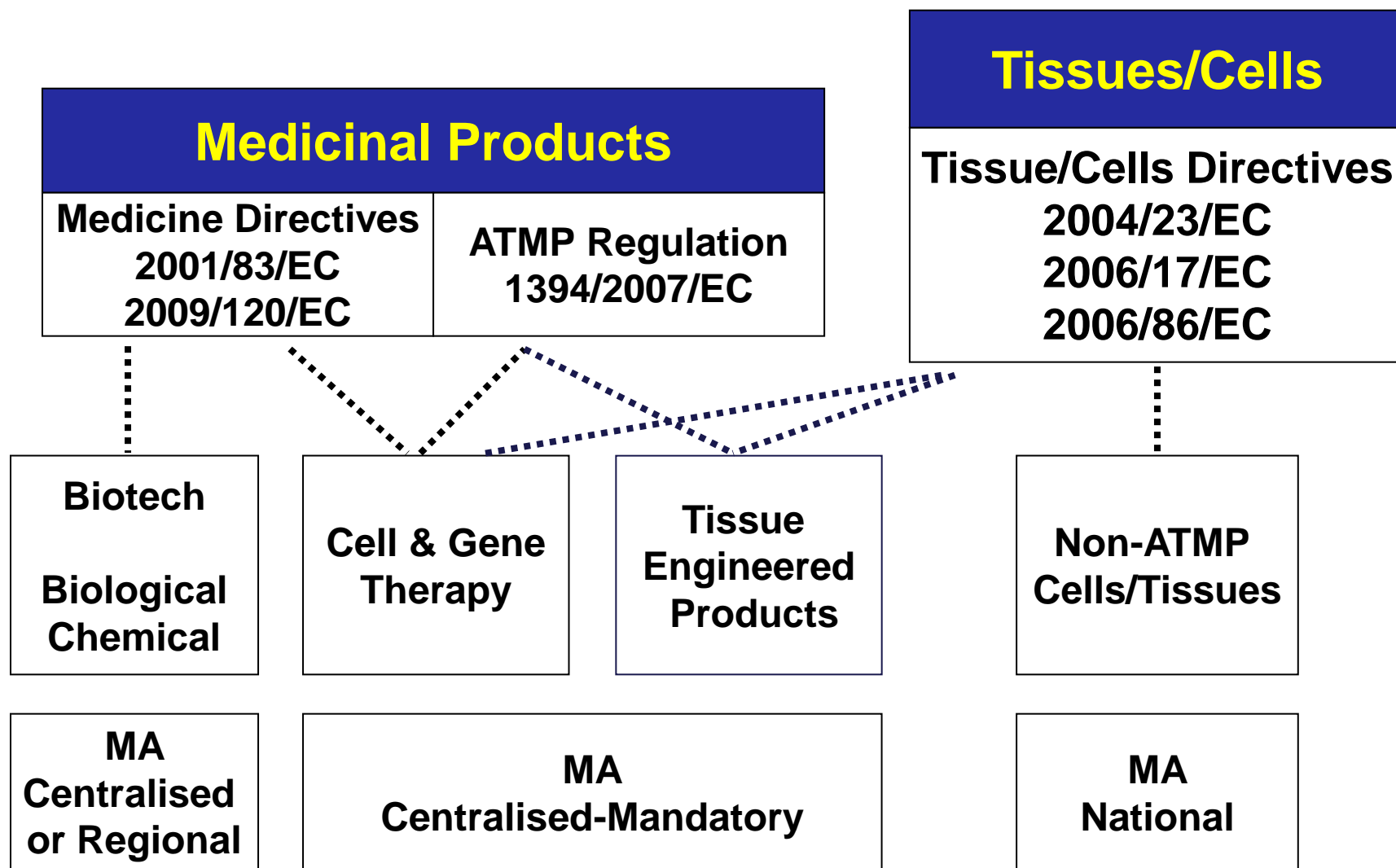


# EU Regulation of Cell and Tissue Therapy Products

- Centralized European marketing authorization for Advanced Therapy Medicinal Products (ATMPs) through Committee for Advanced Therapies (CAT)
  - Somatic cell therapy, gene therapy, tissue-engineered products, combination products
- ATMP clinical trials regulated nationally, policies and requirements specific to each national regulatory agency



# EU Regulatory Framework



# EU Regulatory Framework: Limitations and Response



- Importance of multinational clinical trials - account for 24% of EU clinical trial applications, and majority of trials with >40 subjects
- Current regulatory structure complicated by role of national authorities in authorization/oversight of clinical trials, but EMA CHMP/CAT having responsibility for EU marketing approval, and by varying ATMP experience among different national authorities.
  - From 2007 to 2011, number of clinical trials in EU fell by 25%, and number of clinical trial applications dropped from 5028 to 3800
- Voluntary Harmonization Procedure (VHP) - European Clinical Trial Facilitation Group
- Proposed revision of Clinical Trials Directive, 2001/20/EC
- EU Clinical Trials Register ([www.clinicaltrialsregister.eu](http://www.clinicaltrialsregister.eu))

# Voluntary Harmonisation Procedure (VHP)



- Enables joint assessments of clinical trials and exchanges between national regulators of Member States.
- Voluntary parallel submission of a clinical trial application core dossier to all participating Member States, followed by separate application(s) to national regulators



**Clinical Trials Facilitation Groups**  
**Guidance document for a Voluntary Harmonisation  
Procedure (VHP) for the assessment of multinational  
Clinical Trial Applications**

**Version 2**

*Doc. Ref.: CTFG//VHP/2010/Rev1  
March 2010*



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# Revision of Clinical Trials Directive, 2001/20/EC



- New clinical trial authorisation procedure. Proposal to be discussed in European Parliament and Council, but expected to be effective in 2016.
  - Harmonised authorisation dossier, with ‘single portal’ to submit a clinical trial application, linked to an EU database
  - Flexible and swift assessment procedure, involving all Member States in which trial is to be conducted
  - Mechanism to appoint a reporting Member State
  - Clear timelines with a concept of tacit approval, to ensure compliance
  - Coordination and advisory forum to address issues arising in authorisation procedure
  - Distinction between aspects where Member States cooperate in assessment, and aspects of an intrinsic ethical or national/local nature where assessment is made by each Member State individually
  - Option, in certain well-defined cases, for a Member State to 'opt-out' of conclusions of an assessment of an application for conducting a clinical trial
  - Each Member State defines organisation and internal competencies for assessing clinical trial authorisations, within international guidelines on assessor independence
  - Rapid procedure to ‘extend’ a clinical trial to additional Member States
  - Rules governing when trial modifications after authorisation would require assessment and authorisation of modification



# Guideline on Risk-based Approach



- Identify risks associated with clinical use of the ATMP
- Identify product-specific risk factors contributing to each identified risk
- Map relevant data for each identified risk factor to identified risks – a matrix to evaluate contribution of risk factors to risks
- Conclusions regarding risk factor–risk relationships



19 January 2012  
EMA/CAT/CPWP/686637/2011  
Committee for Advanced Therapies (CAT)

Draft guideline on the risk-based approach according to  
Annex I, part IV of Directive 2001/83/EC applied to  
Advanced Therapy Medicinal Products



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# EMA/EU Guidance Documents



- Guideline on human cell-based medicinal products (EMA/CHMP/410896/06)
- Guideline on safety and efficacy follow-up - risk management of ATMPs (EMA/149995/08)
- Guideline on risk management systems for medicinal products for human use (EMA/CHMP/96268/05)
- Guidance document for a Voluntary Harmonisation Procedure (VHP) for the assessment of multinational Clinical Trial Applications (CTFG//VHP/10)
- Guideline on the minimum quality and non-clinical data for certification of advanced therapy medicinal products (EMA/CAT/486831/08; 2010)
- Procedural advice on the certification of quality and nonclinical data for small and medium sized enterprises developing ATMPs (EMA/CAT/418458/08; 2010)
- Guideline on potency testing of cell-based immunotherapy medicinal products for treatment of cancer (CHMP/BWP/271475/06)
- Points to Consider on xenogeneic cell therapy (CHMP/1199/02)
- Revision of Points to Consider on xenogeneic cell therapy medicinal products (CHMP/165085/07)
- Xenogeneic cell-based medicinal products (CHMP/CPWP/83508/09)
- Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials (EMA/CHMP/BWP/534898/08; 2012)
- Concept paper on the development of a guideline on the risk-based approach according to annex I, part IV of directive 2001/83/EC applied to advanced therapy medicinal products (CHMP/CPWP)708420/09)
- Reflection paper on stem cell-based medicinal products (CAT/571134/09)
- Reflection paper on *in vitro*-cultured chondrocyte containing products for cartilage repair of the knee (CAT/CPWP/288934/09)



# TGA – Code of GMP Revision, Infectious Disease Minimisation Order



- Code of GMP for blood and tissues currently in effect dates from August, 2000
- Revisions in progress to:
  - Code of GMP for human blood and blood components, human tissues and human cellular therapy products
  - Infectious Disease Minimisation Order - Standards for donor selection, testing and minimising infectious disease transmission via therapeutic goods that are human blood and blood components, human tissues and human cellular therapy products
- Unknown timeframe for final approval and publication of revised Code of GMP and Infectious Disease Minimisation Order, but a transition period for revised requirements will apply for approximately 12 months from effective date



# Australian Regulatory Guideline for Biologicals, July 2011



- Appendix 4: Guidance on donor selection, testing and minimising infectious disease transmission via therapeutic goods that are human blood and blood components, human tissues and human cellular therapy products
  - Annex 1, requirements for donor selection, testing and minimising infectious disease transmission which reflect the current position of the TGA in relation to these requirements.
- “Sponsors and manufacturers are strongly advised to consult this document when preparing dossier content or considering operational changes in relation to infectious disease minimisation.”



## Australian Regulatory Guidelines for Biologicals

Appendix 4 – Guidance on donor selection, testing and minimising infectious disease transmission via therapeutic goods that are human blood and blood components, human tissues and human cellular therapy products

Version 1.1, August 2011

TGA Health Safety  
Regulation



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# Data Quality

# EMA Certification of ATMP Quality and Non-clinical Data

COMMISSION REGULATION (EC) No 668/2009

of 24 July 2009

implementing Regulation (EC) No 1394/2007 of the European Parliament and of the Council with regard to the evaluation and certification of quality and non-clinical data relating to advanced therapy medicinal products developed by micro, small and medium-sized enterprises

- Certification by CAT, at any stage of development (although minimum set of data)
  - Data and methodology in compliance with scientific/technical requirements
  - Quality - general information and specifics about starting materials, characterization and control of drug substance, description and composition of product
  - Non-clinical - primary pharmacology data, biodistribution data, toxicology study



# Guidance on Certification of ATMP Quality and Non-clinical Data



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

15 October 2010  
EMA/CAT/418458/2008/corr.  
Committee for advanced therapies (CAT)

Procedural advice on the certification of quality and non-clinical data for small and medium sized enterprises developing advanced therapy medicinal products



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

15 October 2010  
EMA/CAT/486831/2008/corr  
Committee for advanced therapies (CAT)

Guideline on the minimum quality and non-clinical data for certification of advanced therapy medicinal products

Harmonized expectations for terminology and types and quality of data needed for cell therapy products used in multiple jurisdictions (i.e., globalized cell therapy products)

# Guideline on the Requirements for Quality Documentation Concerning Biological Investigational Medicinal Products in Clinical Trials (EMA/CHMP/BWP/534898/2008)

- March, 2012 - adopted by EMA Committee for Medicinal Products for Human Use (CHMP)
- Does not cover ATMP's, but useful points to consider



18 February 2008  
EMA/CHMP/BWP/534898/2008  
Committee for Medicinal Products for Human Use (CHMP)  
Brussels, 03/05/2012  
SANCO/SO/DF.dg1.s.6(2012)632239

Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials

## Information on biological, chemical, and pharmaceutical quality

### Active substance

Manufacturing
Characterisation
Control of active substance
Reference standards or materials
Container closure
Stability

### Investigational product

Description and composition
Development
Manufacturing
Control of excipients, investigational product
Reference standards or materials
Container closure
Stability

### Facilities and equipment

Adventitious agents safety evaluation

Excipients

Solvents for reconstitution, diluents



# Supplemental Slides





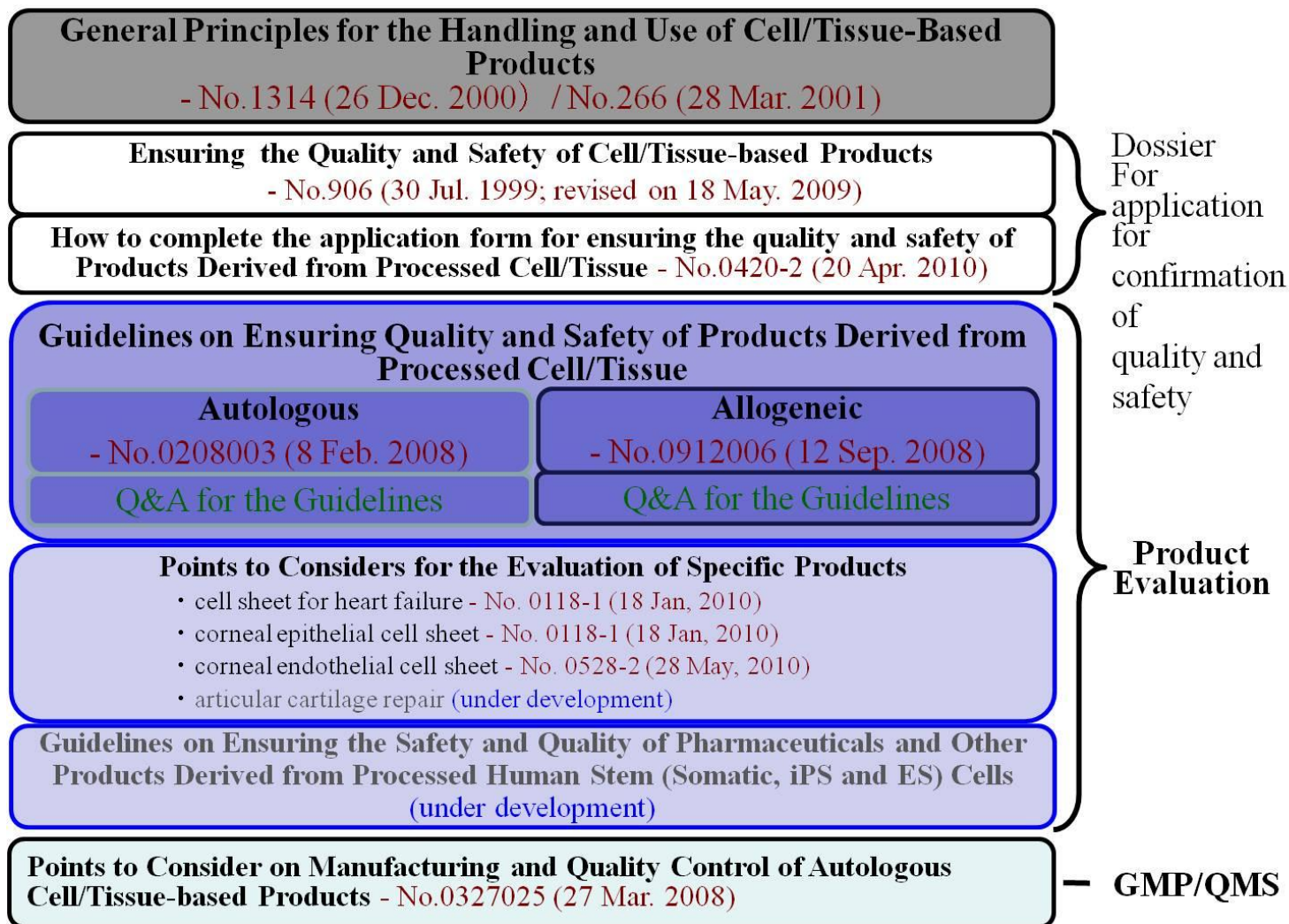
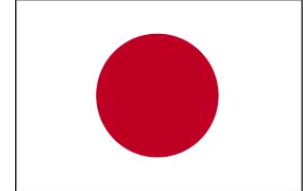
# India



- Developing cell/tissue therapy regulatory framework, resembles US FDA
- Formal regulations regarding cell therapy products said to be before legislature
- Drug Controller General of India (DCGI) regulates clinical trials, but without cell therapy-specific regulations
- Clinical trials of allogeneic adult bone marrow-derived MSCs, other stem cell-based products in progress
- Indian Council for Medical Research (ICMR)
  - Guidelines for Stem Cell Research and Therapy



# Japan



# China



- SFDA
  - Guideline for Study of Human Gene Therapy and Product Quality Control (2003)
  - Guideline for Study of Somatic Cell Therapy and Product Quality Control (2003)
- Minister of Health (MOH)
  - Regulation for Clinical Application of Medical Practices (2009)



# Korea



			Autologous	Allogeneic	Xenogeneic
Cells	<ul style="list-style-type: none"> <li>Minimal manipulation (centrifugation, washing, freezing)</li> </ul>	Hospital	Practice of medicine (Medical Service Act)		Cell therapy products (Pharmaceutical Affairs Act)
		Company			
	<ul style="list-style-type: none"> <li>More than minimal manipulation (expansion &amp; selection, alteration of characteristics)</li> </ul>				
Tissues			Practice of medicine (Medical Service Act)	Human tissues for transplantation (Human Tissue Safety & Control Act)	Xenogeneic tissues
Organs			<del>Practice of medicine (Medical Service Act)</del>	Human organs for transplantation (Human Organ Transplantation Act)	Xenogeneic organs

# Singapore



- Phased-in risk-based regulation of CTT products
  - High-risk CTT products will be regulated first
  - Low-risk CTT products will be regulated in the later phase of CTT regulatory framework
- HSA will regulate the quality, safety and efficacy of high-risk CTT products like other Western medicinal products
  - Clinical trial authorization
  - Product license for marketing
  - GMP for manufacturing facilities, PIC/S GMP standards
  - Serious adverse events reporting and patient registration