“Regulation of ATMP trials in the EU: is it breaking the ‘virtuous circle’?”

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What are the specific regulations covering cell therapies in the EU?

- **2001**
  - 2001-83-EC Medicines Directive
    - Substance includes human blood and blood products
    - Implicit application to human somatic cells

- **2004**
  - Clinical trials directives enacted – include “substantially modified somatic cells” as IMP for the first time. GMP manufacture required plus MA (IMP) and Qualified Person.

- **2006**
  - Tissues & Cells Directives enacted in UK

- **2009**
  - ATMP Regulations published
  - Procurement of starting material regulated by HTA and requiring licence
  - “nonsubstantial” defined
  - Inclusion of HEC for one-off, non-trial products – “non-routine”
  - 2009-120-EC amended 2001-83-EC to included ATMP
What is an ATMP?

An ATMP is a medicinal product as defined in Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (the Directive). Specifically, an ATMP is a biological medicinal product which is either:

- a gene therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC;
- a somatic cell therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC; or
- a tissue engineered product as defined in Article 2 1 (b) of the ATMP Regulation.
Consequences of regulating cells as medicines

- Manufacturing licence needed
- Full GMP – Class 100 in class 100 for “open”
- Clinical trials
  - MA (IMP) **AND QP**
  - IMPD
    - Pre-clinical models
    - Toxicity & biodistribution
  - IB
- Full GCP

Non-trial
- F-I-M – HEC or non-licensed medicine
- Licensed medicine with MA
There different types of cell therapies from a regulatory perspective

- Non medicinal
  - Not “substantially modified”
    - Directly selected anti-viral T cells using multimer reagents
    - Prepared and administered in a single operating procedure

- Medicinal - ATMP
  - Investigational - IMP
  - Unlicensed (“Special” or HEC)
    - Article 5
      - 1. A Member State may, in accordance with legislation in force and to fulfil special needs, exclude from the provisions of this Directive medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised health-care professional and for use by an individual patient under his direct personal responsibility.

- HEC
  - Advanced therapy medicinal products which are prepared on a non-routine basis according to specific quality standards, and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient.

- Licensed
  - ChondroCelect, Provenge, HemaCord

- Borderline
Cell therapy MP examples at UCLP

ATMPs are MOSTLY single named donor:single named recipient (cf transplant products)
Very rarely single donor: multiple recipient (cf blood products)
Very very rarely multiple donor: single or multiple recipient (cf conventional pharmaceuticals)

NB – 1 BATCH = 1 PRODUCT

• Simple ATMP
  – Antigenically stimulated lymphocytes for adoptive immunotherapy
    • CMV-R T cells by gamma-catch – “open” process
    • CTV-1 primed NK cells – “open” process

• Complex ATMP
  – Mesenchymal stem cells – “open” process involving single donor
    • Undifferentiated
    • Differentiated
  – Limbal stem cells – “open” process involving single autologous donor
  – HuESC-derived RPE
  – Re-cellularised donor trachea for transplantation – “open” process involving 2 donors (1 cadaveric)
  – Genetically modified T cells – “open” process involving single autologous donor and cGMP gene product
    • Suicide gene insert
    • Modified TCR insert
  – Cell:device combination
    • MSC-chondrocytes with bio-compatible synthetic support matrix
What are the current limitations?

• Common lack of relevant pre-clinical models
• Rare availability of GMP-compliant reagents for manufacturing
• Very novel field so equipment is lacking
• Regulations designed for batch processing rather than single product:single patient
• First-in-Man (phase I) very commonly First-in-Patient (phase I/II)
• Often small market but critical unmet need – F-I-M studies tend to be academia initiated and sponsored
• At least phase I/II data needed before moving into biotec/biophama arena
• Pre-clinical data difficult to obtain to produce IMPD for clinical trial submission
• Shortage of QP across EU
EU scoping questionnaire:

Academic-based manufacturing in the EU:

- non-ATMP stem cell products for transplantation: 48%
- stem cell products as ATMPs (e.g. Mesenchymal stem cells): 45%
- gene transfer medicinal products: 20%
- embryonic stem cell products: 5%
- tissue engineered products/cells on a scaffold: 27%
- non genetically modified somatic cells as ATMPs: 44%
ATMP development in the EU

• EU commission needs
  – Protection of the public
  – Increased academic output
  – Increased industrial development of ATMP
  – Increased GDP from ATMP

• Reality
  – Academia is driving ATMP development but held back by regulation
  – Commercialisation of ATMP will be ESSENTIAL for maximum treatment availability
  – Commercialisation DOES NOT require marketing authorisation – unlicensed medicines
  – Current trials legislation is aimed at MA – some ATMP may never meet MA standard but are clinically effective and valuable
All are interdependent:

1. Clinician wants to innovate treatments and NEEDS patients
2. University NEEDS high impact publication and IP but not to fund phase III trials for MA
3. Industry NEEDS clinician to innovate and University to support proof-of-principle and reverse translation
4. University NEEDS Industry to buy its IP and commercialise it after clinical trials
5. EU Commission NEEDS to ensure patient safety and maximum availability of novel therapies and commercialisation
6. Patients need access to new, safe and effective treatments
Is current clinical trials legislation appropriate for ATMPs?

- Intended to result in a MA
  - A fixed manufacturing process which delivers a reproducible product with established safety profile and efficacy
- ChondroCelect – first and only ATMP with MA in EU
- 4 MA in US already

Questions
- What proportion of ATMPs in development are “patient-directed”?
- Is the traditional MA-route appropriate for most or even many of these?
- What about supply as “non-licensed” medicines?
  - Re-imbursement for manufacture
  - No advertising of product
  - No clinical trials (?) – No IMPD
  - Existing pharmacovigilance process
  - Exportable
  - How do you prove efficacy?
How might we improve the pipeline for ATMPs which should obtain MA?

**EU legislation level**
- Facilitate phase I/II trials
  - More precise definition of the quality requirements for an IMPD
  - Acceptance that animal models may be inappropriate
  - Recognise that this field is important for EU GDP but is currently >90% academic led
    - Support small academic GMP facilities (move to FDA risk-based approach?)
    - Create “GTP” standard to align with FDA “A in a C background”
    - Increase availability of EDQM reagents for manufacturing

**EU university and funding body level**
- Invest in translational research beyond F-I-M
  - FIM is “cheap” and gets high impact publication (unethical?)
  - Phase III trial needed before commercial funding likely so no early “spin outs”
  - GMP & GCP resources needed for academics (radical limitation of this work?)

**Academic PIs**
- Open exchange of SOPs and reagent qualifications
- Frank and honest reporting of non-trial F-I-M results (data registry?)
CAT should reflect, when non-clinical studies are requested, on how far knowledge from previous clinical experience can be taken into account.

Clinical data may compensate for non-clinical studies (depends on quality/source of data/risks).

Use of smart in-vitro testing may in certain cases potentially complement or even substitute animal studies.

Lowdell, Thrasher & Birchall (2012) – Use of FIM ATMP studies to provide pre-clinical data for CTA. Lancet (in press)
• Addressing unmet clinical need by ethical FIM – unlicensed medicines
  – GMP manufacture to ensure reproducibility and comparability
  – Documented clinical risk assessment
  – Documented product risk assessment
  – SAE/R reporting structure to MHRA
• Small & large animal facility for conventional pre-clinical modelling
• Compilation of pre-clinical data for IMPD
• Faculty-funded specialist clinical trials personnel for ATMPs
  – CTA assistance
  – GCP assistance
  – GMP co-ordination
• In-house GMP units for ATMPs
  – RFH / IoO / ICH / Bloomsbury vector unit
• In-house clinical GLP labs for trial monitoring
• In-house CTU with CRAs

EXPENSIVE AND UNDER THREAT
• “Studies” – not trials
  – CMV-specific immune regeneration post HSCT - PhI/II and PhIII
  – Allogeneic MSC infusions for severe GvHD – PhI/II
  – ProT4 DLI for relapse post allow HSCT – PhIII multicentre

• Clinical Trial
  – Allogeneic primed NK cell therapy for AML – PhI/II

• First-in-Man – not trials and never aimed at MA
  – Autologous stem cell seeded cadaveric tracheal transplant
  – Autologous stem cell-derived cell seeded biocompatible tissue structure for tracheal transplant
  – Autologous stem cell-derived cell seeded biocompatible tissue structure for nasal reconstruction
Conclusions

• >75% of ATMP trials in EU are academic-initiated and manufactured DESPITE legislation

• Extremely difficult to design and run trials
  – ATMP requires IMPD and CTA & QP

• Complex ATMPs (even 3-D tissue/cell constructs) can be manufactured to GMP in academia and SME

• ATMPs are already providing cost-effective clinical solutions in some cases

• Seemingly unattractive to conventional pharma due to supply chain and reimbursement questions

• Need to work with legislators, regulators, funding bodies, universities and commercial sector to develop this field WITH PATIENTS
Acknowledgements

- Stephen Mackinnon
- Karl Peggs
- Panos Kottaridis
- Martin Birchall
- Alex Sefalian
- Martin Elliott
- Paolo Macchiarini
- Paolo DeCoppi

- Maryam Sekhavat
- Fiona O’Brien
- Janet North
- Ed Samuel
- Carla Carvalho
- Leanne Partington
- Ismail Bakhsh

- Martin Hildebrandt & consortium
- Elaine Godfrey / Ian Rees

- EU FP7
- MRC
- LLR
- UCL BRC
- NIHR

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