Regulatory and Scientific Considerations on Adoptive Cell Immunotherapies: The View of the Committee for Advanced Therapies

World ADOPT Summit 2017- Adoptive Cell Immunotherapies

Christiane Niederlaender, CAT Delegate, MHRA
CD19 CAR-T cells
Sustained remissions in refractory leukemia

CD19 CAR-T cells

Fatal events

“Deaths in CAR-T Trials Haunt Promising New Cancer Treatment”
Cancer Immunotherapies: Increasing Armentarium

- CTLA-4 inhibitors
- PD-L1 inhibitors
- Monoclonal antibodies
- Blinatumomab (BITE)
- Sipuleucel-T (Advanced Therapy MP)
- T-Vec (oncolytic virus) (ATMP)
Cancer Immunotherapies Increasing Armentarium

Marketing Authorisations

Clinical trials

CTLA-4 inhibitors
PD-L1 inhibitors

--- 2011 2013 2015 2016 ---

Monoclonal antibodies
CTLA-4 inhibitors

Blinatumumab (BITE)
PD-L1 inhibitors

Sipuleucel-T Advanced Therapy MP
T-Vec (oncolytic virus) ATMP

Multi-peptide-based
Genetically modified bacteria

Viral vector-based
CAR-modified Tcells

mRNA-based
TCR-modified Tcells

Marketing Authorisations

Clinical trials
Assessing Cancer immunotherapy products
Cells as pharmaceuticals: Complexity of the active ingredient

- Signalling
- Morphology
- Functionality
- Gene expression
- Energy
- Motility
- Respiration
- Quality of proteins
- Differentiation
- Proliferation
- Apoptosis
- Integrity of organelles
- Metabolic activity
- Viability
- Respiration
- Energy
- Morphology
- Functionality
- Gene expression
Cell-based cancer immunotherapies: Complexity of manufacturing process

Apheresis → Cell preparation → Gene transfer → Cell expansion → Formulation, storage

Vector/GT/ raw material production → Vector/GT/ raw material testing

Quality, Safety and Efficacy are interlinked!
The EU legal & regulatory framework for ATMPs: Complexity?

- Blood: 2002/98/EC
- Tissues/Cells: 2004/23/EC
- PhVig legislation: Dir. 2010/84/EU and Reg. 1235/2010
- Clinical Trials: 2001/20/EC
- Paediatrics: 1901/2006
- Advanced Therapy Regulation: 1394/2007
- Medicinal Products: Dir. 2001/83/EC and Centralised procedure: Reg. 726/2004
- GMO legislation: Directives 2001/18/EC and 2009/41/EC
- Medical Devices: 93/42/EC and 90/385/EC
- GMP: 2003/94/EC
- Orphans: 141/2000
- Variations: 1084(5)/2003 and 1234/2008

- Falsified Med.: Dir. 2011/62/EU
Challenges
View of a Developer/applicant

• Understanding the EU regulatory system

• Transferring manufacturing to EU facilities – comparability

• Dealing with different players/authorities in regulatory system
  – GMP certificate
  – Clinical trial authorisation
  – Marketing authorisation
European and US regulators agree on mutual recognition of inspections of medicines manufacturers

- Transatlantic agreement will help to make better use of inspection capacity and reduce duplication

Regulators in the European Union (EU) and the United States (US) have agreed to recognise inspections of manufacturing sites for human medicines conducted in their respective territories on both sides of the Atlantic.
Advanced Therapy Medicinal Products (ATMPs)

Gene Therapy Medicinal Products

Somatic Cell Therapy Medicinal Products

Tissue Engineering Products

Genetically modified cells

medical device + ATMP → combined ATMP
Centralized Marketing Authorisation obligatory for ATMPs

Scientific advice (national and/or EMA), certification

Development ➔ Preclinical ➔ Clinical trials PhI PhII PhIII ➔ MAA Review ➔ Post Marketing

- GMO application
- GMP
- CT application (national authorities)
- Pre MAA Meetings (Rapp & Co-Rapp)
- PSUR cycle
- CE marking/
  Evaluation of structural Component(s) by Notified Body
EMA Committees for ATMPs

CAT
Chair: M. Schuessler-Lenz

18 quality experts
12 non-clinical experts
21 clinical experts (including 4 members representing physicians)
4 patient representatives
8 other (scientists, heads of departments etc.)

Total 68 experts

CHMP
Chair: T. Salmonsson

Overview of CAT expertise

- Cell Therapy: 26%
- Tissue Engineering: 15%
- Gene Therapy: 17%
- Surgery: 1%
- Biotech: 19%
- Ethics: 11%
- Phvig Med Dev: 5%
- Surgery: 6%

5 „double members“
Way of building the evidence – applicable for innovative products?

- Conditional MA
- Adaptive Pathways
- PRIME
- Registries
- Real World Data
- HTA and reimbursement
Risk-based approach

- Prospectively planned strategy to justify the need for data in the MAA, *proportionate requirements based on risks*

- Does **not provide a rigid classification system** of different risks of a product as whole (e.g. high-risk product vs. low-risk product)

- Is intended to provide **flexibility** to regulation of ATMPs

- Should help developers to overcome challenges due to the specific nature of the ATMPs

- How to do the risk/risk factor profiling?
  
  → GL on risk-based approach (EMA/CAT/CPWP/686637/2011)
  → Q/A document on RBA under preparation
  → scientific advice
Adaptive Pathways

1. Iterative development either of:

   a. staggered approval from initially restricted patient population to increasingly wider populations

   b. confirmation of the benefit/risk balance of a product authorised under Conditional MA with early or surrogate endpoints.

2. Gathering of evidence through real-world data to supplement clinical trial data

3. Involvement of patients and health technology assessment (HTA) bodies in the discussion of the product development program.

   ‘Safe harbour’ discussions – formalisation of advice via normal SA procedure.
PRIME (Priority Medicines)
Early access tool, supporting patient access to innovative medicines

- To foster development of medicines with a high public health potential
  - Reinforced scientific and regulatory advice
  - Optimise development for robust data generation
  - Enable accelerated assessment

- Eligibility to PRIME:
  - Potential to address an unmet medical need
  - Scientific justification based on data / evidence from non-clinical and clinical development

Features

- Written confirmation of PRIME eligibility and potential for accelerated assessment;
- Early CHMP/CAT Rapporteur appointment during development;
- Kick off meeting with multidisciplinary expertise from EU network;
- Enhanced scientific advice at key development milestones/decision points;
- EMA dedicated contact point;
- Fee incentives for SMEs and academics on Scientific Advice requests.
Kick-off meeting - starting point to discuss regulatory strategy

Regulatory
- Milestones leading to accelerated review of marketing authorisation application
- Interaction with Pediatric Committee, status of pediatric investigation plan (PIP)
- Interaction with Orphan Committee, orphan similarity

Quality, non-clinical, clinical issues

Postmarketing
- Risk management plan
- Registries
If PRIME is not the right tool

EMA still can provide support through...

- EU innovation network
- Innovation Task Force
- Scientific Advice
- SME office
- ATMP certification
- Paediatric early interaction meetings
- Accelerated Assessment
- Pre-submission meetings
Available EU guidance for cell-based immunotherapies

Guideline on cell-based medicinal products (2008)

Guideline on the Risk-based approach (2013)

Follow-up of patients administered with gene therapy medicinal products

Potency testing of cell-based immunotherapy MPs for treatment of cancer (2007)

Non-Clinical testing for Inadvertent Germline transmission of Gene Transfer Vectors

Quality, preclinical and clinical aspects of gene therapy medicinal products (2017/Q?)

Guideline on MPs containing genetically modified cells

Reflection paper on stem-cell based MPs

Scientific Requirements for the Environmental Risk Assessment of Gene Therapy Medicinal Products

Development and Manufacture of Lentiviral Vectors

Non-clinical studies required before first clinical use of gene therapy medicinal products

Manufacturing challenges

- Multi-Donor product
- Complex manufacture of Raw materials
- Development and relevance of potency assay
- Release testing of product with short shelf-life
- Assay development: bridging studies
- Manufacturing process changes: comparability
- Multi-site manufacture: Comparability
- High level of manipulation vs Automation?
- Partial Manufacture vs administration site reconstitution
Comparability testing – what does it mean?

- Change of manufacturing sites, other modifications to the process
- Changes made to the production process, materials, etc. could lead to clinically significant changes in the final product
- Critical parameters
- Level of testing (release + characterisation), stability testing
- How to interpret differences?
- When are quality data alone sufficient to demonstrate comparability of cells?

CAT to start drafting Guideline on Comparability for cell-based products in 2017
Clinical Trials with CAR-T cells

188 ongoing trials world wide (10/2016)

121 for lymphoma, leukemia
60 for solid tumors
9 long-term follow-up studies

13 trials in Europe
## CAR/TCR-modified T cells

### Activities in European Union - Examples

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Regulatory Guidance Clinical
Challenges Clinical Trial Authorisation – Benefit-Risk Assessment

- Variability
  - product, patients, trial features

- Low predictability of toxicity
  - Onset
  - Severity
  - Course – duration of patient hospitalisation
  - Link to efficacy (double edged sword)

- Qualification of EU trial centres
  - Transplant centres
  - Training of involved personnel
Clinical and regulatory challenges in the development of Adoptive Cell Immunotherapies in EU

Conclusions

• Differences between products require case-by-case decisions
• Iterative discussions and exchange of information is needed between scientists, physicians, developers, regulators
• Unmet medical need - regulatory path requires tailored approach
• Best way forward in the EU regulatory system to enable and foster patient access?
Thank you!