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Introduction

Riset consortium activities on reprogramming the immune system for establishing tolerance in transplantation covers aspects from fundamental research to pilot clinical assays involving cell therapy, in the context of transplantation.

The regulatory framework of such a wide scope is evolving quickly and is regularly scrutinized in order to update the consortium on new relevant texts at legal, regulatory and ethical levels.

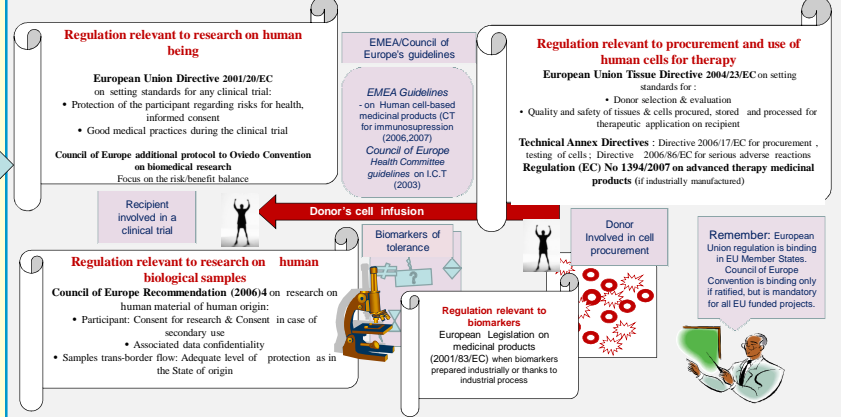
Schematically there are a number of institutional levels to consider both for transplantation and for cell therapy ; The Figure illustrates the major texts that apply to these activities at Council of Europe and European Union level.

Specific attention has been paid in 2007 to 2 relevant sets of recommendations in preparation by EMEA: the European Medicine Agency, <http://www.emea.europa.eu/>.

Schematic overview of regulations that are relevant for tolerance induction clinical pilot assays involving cell therapy and tolerance biomarkers validation

Immune cell therapies implying the use and assessment of biomarkers of tolerance are still clinical research therapies used in the field of transplantation. Researchers of the Riset consortium are working in this field. The characteristics of the current pilot clinical assays rely on the use of the donor's cells to induce tolerance, sometimes involving an iterative procurement. The living donor gives both cells for tolerizing and the graft itself (organ, tissues or cells; kidney, bone marrow, liver). These cells are transformed in order to induce tolerance to the graft in the recipient who will be either waved from immunosuppression or with reduced regime. During monitoring biomarkers of tolerance are assessed or used as elements of follow up if already validated.

HOW DOES EUROPEAN REGULATION DEALS WITH THIS THERAPIES RELATED TO TRANSPLANTATION ?



EMEA

EMEA is The European Medicine Agency (London)

- Field of Competences:
 - Protection and promotion of public & animal health
- Main tasks
 - Safety of medicines through a constant monitoring of a pharmacovigilance network within European Union
 - Scientific advice for the development of new medicinal products
- Consists of different committees such as CHMP (Committee on Human Medicinal Products)
- CHMP:** Committee on Human Medicinal Products
- Assessments** conducted by the CHMP
 - are based on purely **scientific criteria**
 - **determine whether or not the products concerned meet the necessary quality, safety and efficacy requirements** (in accordance with EU legislation).
- These processes ensure that medicinal products have a positive risk-benefit balance in favour of patients/users of these products once they reach the marketplace.**
- Guidelines prepared by working groups undergo open public consultation prior to finalisation: professionals groups as Riset consortium can comment and may thus influence the process.**

EMEA 1. Draft Guidelines on human cell based medicinal products *

Scope:

- Development, Manufacturing and quality control as well as non-clinical and clinical development of cell-based medicinal products
- Cell-based medicinal products (CBMP)
 - *Viable human cell of allogeneic or autologous origin undergoing a manufacturing process
 - *Might be combined with non-cellular components
 - *Might be genetically modified

Relevance in accordance with EU Directive (Directive 2004/23/EC)

- Risk analysis
- Quality and manufacturing aspects
- Development pharmaceuticals
- Traceability and biovigilance
- Comparability
- Non-clinical development
- Clinical development: General aspects, Pharmacodynamics, Pharmacokinetics, Dose finding studies, Clinical Efficacy, Clinical safety, Pharmacovigilance and Risk management

Riset Comments

- Document very positively received: useful, reasonable and well documented
- Insist on reproducibility among different samples
- Fully test the final sample cell preparation product, while limiting the tests done for each single patient preparation
- Avoid that the amount of product dedicated to pharmacological testing and quality controls becomes bigger than that needed for treatment.
- Tumourigenicity is an important aspect of cellular therapy and could be more clearly underlined.
- Risk analysis chapter most useful as a reference for research ethics committees.

* Doc. Ref. EMEA/CHMP/410869/2006, open to comments from 25/01/ 2007 to 31/07/ 2007. <http://www.emea.europa.eu/pdfs/human/cmpw/41086906en.pdf>

EMEA 2. Draft guideline on clinical investigation of immunosuppressants for solid organ transplantation **

Scope:

- Defining treatment goals, study designs, outcome measures and data analysis for new immunosuppressive products developed to prevent and treat solid organ allograft rejection
- Selective immunosuppressant regimen : an optimal balance between beneficial immunosuppression of immune reaction leading to rejection on one hand side, and over-immunosuppression which can cause increased risks of infections and malignancies on the other.

Relevance in accordance with EU Directive on Medicinal Products (Directive 2001/83/EC) & specific European legislation

- **Subject characteristics and selection of subjects:** for recipients and donor + transplant
- **Methods to assess efficacy:** Definition of primary endpoints for induction, initial and/or maintenance prophylaxis, acute rejection treatment, definition of secondary endpoints for graft function at various time points, graft survival at various time points, patients survival at various time points, incidence and/or time to biopsy-proven first acute rejection...
- **Strategy and design of clinical trials:** Pharmacokinetics, Pharmacodynamics, Therapeutic studies (exploratory trials, confirmatory trials, methodological considerations)
- **Clinical safety evaluation:** General considerations, Specific adverse events

Riset comments

- Importance to underline more strongly
 - the importance of issues related to quality of life of patients,
 - the specificities of living donors and their follow-up
 - specific aspects in patients with cancers

** Doc. Ref. CHMP/EWP/263148/06 ; open on 19/07/ 2007 –to 31/01/ 2008). <http://www.emea.europa.eu/pdfs/human/ewp/26314806endraft.pdf>

Conclusion

Important to include in the activities of a scientific EU consortium proactive reactivity regarding the preparation of regulatory texts that can only be improved if the concerned professionals take the responsibility to comment during their preparation.