Planning for a Trial and Approval Process in Europe

Overview and Guidelines for First in Human Trial for Gene and Cell Therapy

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Procedure for starting a clinical trial in EU

• Overview of the current situation

- ATMP are medicinal products (directive 2001/83/EC)
- Prepared industrially or manufactured by a method involving an industrial process
- CTs for ATMP should follow the CT directive (2001/20CE)
  - GCP directive
  - GMP directive
  - CTD guidances
    - CT1: CTA process and dossier
    - CT3: CT safety
    - Ethics committees (EC)
    - The 2 databases (EudraCT – EV CTM)
EU regulatory framework: stakeholders

European Commission/ad hoc CT working group (NCAs+ECs)

Harmonisation CTD guidances

Dir 2001/20/CE

Heads of Medicines Agencies/Clinical trials facilitation group (CTFG)

Harmonisation Procedures and decisions

Clinical Trial remains on the remit of the NCA
- For the clinical trial approval
- For inspection and
- For EC opinion

NCA: national competent authority
EC: ethical committee
Procedure for starting a clinical trial in EU

Sponsor
1. EudraCT Number
2. Dossier

Ethics committee

Single positive opinion

Authorisation

National Competent Authority

Start of CT

GT timeline 90+30/90 days

CT timeline 90+30/90 days

GMO 120 days
Multi-national Clinical Trial Applications (CTA) are assessed in each MS:

- by several Competent Authorities independently:
  - in parallel and/or
  - one after each other, dependent on the submission date of the applicant
- by several Ethics Committees independently

Consequently:

- Divergent decisions (approvals/conditional approvals/refusals) may be reached for the same clinical trial by different Member States;
Difficulties of this procedure for ATMP sponsors

- Sponsors are often small companies
- The regulatory framework is often obscure for these companies
- Clinical trial with small populations
- The products developed are often complexes
- These difficulties and the divergent opinion of the NCA should impaired the development of these products
The VHP : a way for ATMP ?

• For Multinational clinical trials (2 countries minimum)

• A simple administrative procedure:
  ● Same dossier (protocol, IMPD, investigators brochure, scientific advice/PIP)
  ● Electronic submission, English mandatory

• A standardised procedure for coordinated scientific assessment
  ● Voluntary basis
    ❖ For sponsors
    ❖ For NCA
  ● A leading CA identified : Only one list of GNA, if any.
  ● Includes also substantial amendments
  ● Reliable timelines for sponsors and CA

• GNA : ground for non acceptance
The VHP: a way for ATMP?

- **Step 1:**
  - Request by the sponsor to the VHP coordinator (Paul Erlich Institute - Germany) (PEI)

- **Step 2:** the assessment phase
  - Centralized recevability
  - Review of the Dossier by all the participating countries and a list of questions coordinated by the leading Member State
  - 1st common position around D60, total period maximum 90 days
  - Administrative co-ordination by the VHP coordinator (PEI)

- **Step 3:** the national step
  - Formal approval by each NCAs within short timelines (after positive VHP) around 10 days (except for GMO)
The VHP: a way for ATMP?

- For the sponsors:
  - Harmonisation of the assessment and harmonisation of the final decision through member state concerned
  - Improved timeline for CT approval (1 shot /several approvals)

- For NCA:
  - Harmonisation of the assessment (questions are often discussed before approval)
  - Lead to facilitate the development of promising product in EU

- The HMaS CTFG voluntary harmonisation procedure (VHP) http://www.hma.eu/78.html

- Contact and submissions:
  - VHP-CTFG@VHP-CTFG.EU
Overview and Guidelines for first in Human Trials

General rules:

Non clinical studies : for what purposes ?

Main purposes : to gain knowledge on the product / not to provide regulatory data

Improve knowledge on the product via:
- validation of the proof of concept (Biodistribution studies, mechanism of action, potential adverse events)
- obtained bio-safety data
Overview and Guidelines for first in Human Trials

- **Guidelines**: EU, National or International
  - EU: Mother guideline for Cells and Gene Therapy should be helpful
  - EU: specific guideline (first in man) should help the sponsors in the design of their non clinical development plan
  - EU: Germline transmission
  - EU: risk-based approach should be taken into account in the design of the non clinical development plan

- Objectives of these guidelines: provide general rules

- The current guidelines are usually sufficient
Overview and Guidelines for first in Human Trials

Based on the information gained during the validation of the proof on concept studies the sponsor should design a non-clinical development plan via:

- animal (relevant animal model or surrogate animal model)
- In vitro studies
- Specific animal models developed for a particular disease (for some myopathies)

ATMP currently a case by case approach but the non-clinical development should be conform to the medicinal products requirements

- GLP/GLP principles,
- Same product as for clinical trial (manufactured according to GMP),
- Same procedure of administration in animal studies as for the CT
Overview and Guidelines for first in Human Trials

Gene therapy medicinal products including genetically modified cells: some keys points
- Biodistribution studies should provide information for toxicology, shedding
- Insertional mutagenesis (depending on the vector)
- Germline transmission (depending on the vector)

Cells therapy medicinal products: some keys points
- Biodistribution studies should provide information on trafficking and homing (importance to develop relevant markers and tools)
- Karyotypics anomalies
- Stability of the differentiated cells in case of cells line/stem cells
Conclusions

ATMP new products need to seek advices early from Regulatory authorities

- with EMA: CAT classification, ITF, scientific advice (90% reduction fees for SMEs),
- with the National Competent Authority: in most countries scientific advices are usually free
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◆ This speech is made under strict compliance with the independence and impartiality of ANSM as regards other speakers
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- EMA/CAT/GTWP/671639/2008 Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells
- EMEA/CHMP/GTWP/125459/2006 Guideline on the Non-Clinical Studies Required Before First Clinical Use of Gene Therapy Medicinal Products
- EMEA/CHMP/410869/2006 Guideline on Human Cell-Based Medicinal Products