International Regulatory Forum of Human Cell Therapy and Gene Therapy Products, in Osaka, JAPAN

Overall (Tentative) Summary IRF2016

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Common objectives

- Recognize: emerging new products and developments in the world in Canada, EU, Korea, Japan and US, etc.....
- Acknowledge: opportunities for new product developments and collaboration among regulators, industry and academic societies
- Realize: collectively support for providing safe and effective products, benefiting patients globally
- Share: common challenges of HCTp/GTp regulations from international perspective.

Key Note Lectures

- **FDA's regulations for HCT/p**
  - PHS361 and 351
  - Combination products (designation, offices in charge)
  - Expedited Program available (First Track, BT, Accelerated Approval, Priority Review)
- **EMA/EU regulations for ATMP**
  - ATMP Class , MA and clinical trials supervision system
  - CAT structure and tasks, (approved 6 products so far, Scientific advice : 185)
  - Reflection paper on classification (substantial manipulation, ….)
  - Specific Issues for ATMPs : frontline becomes older, unknown risk, robust prospective evidence, comparability, animal model availability….building evidences, long term follow-up
  - Expedited program (Adaptive pathways, PRIME, conditional)
  - Early contact to RA recommended, risk-based approach, flexibility

Challenges overview: Pre-clinical

- An in-vivo safety study not always relevant for human specificity, feasibility….(existing clinical experiences,…….)
- Difficult to set up universal design of pre-clinical testing (unlike medicines) due to limitations; immunocompromised, healthy/disease animal, way of dosing (microenvironment, volume)…….
- Consider range of ingredients (including cells, scaffold, residual media-impurities) to be covered

Challenges overview: Pre-clinical

- Despite difficulty and challenges, may also provide information proof of concept/mechanism of action, potential safety, human dosing, bio distribution……..in a different way from medicines
- in vivo tumorigenicity study is a challenge, necessity and limitation be recognized, but no internationally accepted guidance:

Challenges overview: CMC

- Difficulty of specification setting due to cell product variability, in process control and verification for quality assurance
- Potency as CQA assay (quantitative) based on MoA, PoC, supporting prediction of effect will be ideal,
  - ➢ but not usually well understood in early phase. Generate data and to be refined in later phase. (seems common in different regions)
  - ➢ may result in biological specific profiles (e.g. phenotype-specific markers) for HCTp nature, matrix approach

May need new definition for HCTP?

Challenges overview: CMC

- Flexibility of microbiological control: HCTp specific environmental contamination, shelf life before administration, volume available……limitations
- Raw material controls such as CQA, traceablility, virus validation…. must be considered, however needs harmonization.
- Challenges of cells as well as vectors to modify genetic sequences to be controlled: qualification, RCV, post-manufacturing release, individualized qualifications

Challenges overview:
Clinical/regulatory interpretation

- Flexible clinical study approaches for cell therapy products, however, implementations may differ from region to region; e.x. clinical designs of HCTPs requires additional considerations, which may be affected; by invasive tissue harvest and implantation, autologous, allogenic, philosophy, feasibility in the region.
- Discussions for adaptive change and challenge for more suitable regulations of HCTPs to secure early clinical access (standard development/dissemination, handling autologous, clinical trial oversight)

Regulatory Climate and Landscape

- We found majority of the regulatory practices and scientific approaches to HCTp are common across the region.
- Consider: emerging regulations different areas; certain commonality and differences (such as classification, RMP, autologous, accelerated process)
- Promote: Risk based flexibility for regulatory requirements (individual case by case basis) due to diversity of products
- Encourage: Scientific alignments among regulatory authorities through international fora (IPRF, APEC, …….)

Challenges

- Convergence rather than harmonization
- Continue: collectively leverage global best practices
- Minimize: inconsistent guidance internationally
- Be aware : common recognition, such as "minimum consensus package" (essential scientific elements of common studies across products) for Global Dossiers (not harmonization of guideline) may be useful

through WHO, IPRF, ASEAN, any international framework?

Thank you very much for your participations today and hard working to realize this successful convergence in Osaka

Continue Working together!
(regulators, industry and academia, internationally)