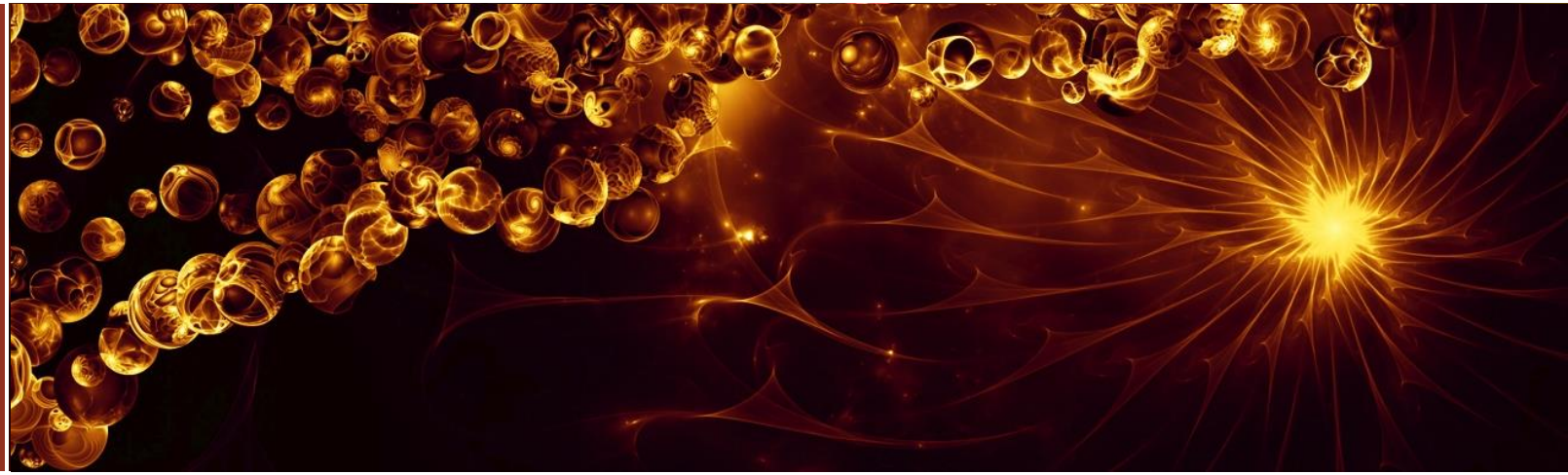

ATMP Development Challenges: From Scientific Advice to Market Authorisation

EMA-EuropaBio Information Day
London, UK

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PHARMACEUTICALS

Cell & gene therapies are key to the future of the pharmaceutical industry

Small Molecules

Chemical engineering

Synthesize small molecules with specific targets

Biologics

Protein engineering

Develop optimized recombinant proteins

(20-30 years ago)

Cell & Gene Therapies

Cellular Engineering

Recode cells to fight against deadly diseases

(today)

Potential to cure cancer, through individualized cell re-programming

Cell & gene therapies are being investigated in disease areas with critical unmet medical needs

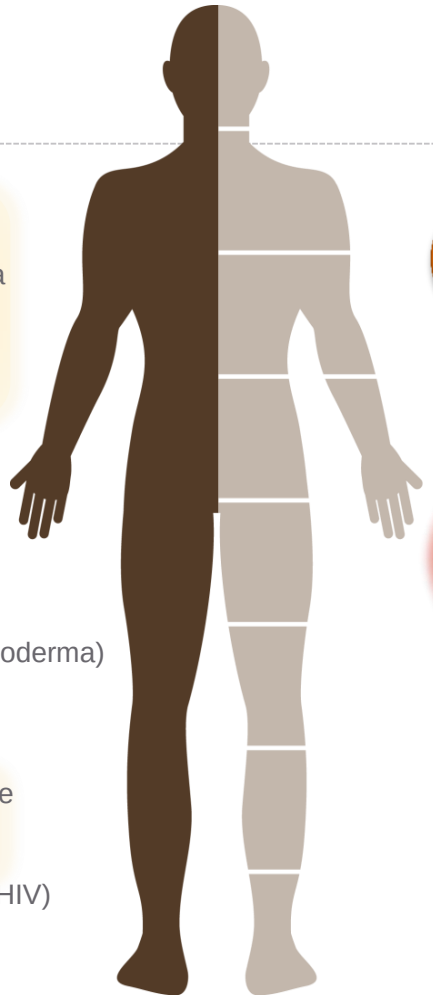
NOT EXHAUSTIVE

Immunotherapies

Cancer
– Hematology
  - Leukemia/Lymphoma
  - Myeloma
– Solid Tumors
  - Pancreatic
  - Ovarian

Autoimmune disease
– Type 1 diabetes
– Rheumatoid Arthritis
– Psoriasis
– Systemic Sclerosis (scleroderma)
– MS, ALS

Others
– Graft versus Host Disease
  - Tissue/Cell Rejection
  - Organ Rejection
– Infectious Disease (e.g., HIV)



Regenerative Medicines

Degenerative Disease
– Neurodegenerative disease (e.g., Alzheimer's, Parkinson's)
– Musculoskeletal (i.e., Muscular Dystrophy)
– Macular Degenerative Diseases

Genetic disorder
– Inborn Metabolic Disorder
– Cystic Fibrosis
– Thalassemia
– Sickle Cell Disease

Others
– Spinal Cord Injuries
– Stroke
– Hearing Loss
– Cardiovascular Disease
– Aplastic Anemia
– Severe Skin Wounds

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Developing ATMPs is complex

Technical obstacles and uncertainties

- Challenges towards adequate animal models for pre-clinical testing
- Historically developed in academic environment without the objective of global commercialisation
- Lacking sensitive tools to extensively characterise the product
- Need for adaptation to reach consistent manufacturing technologies in GMP environment
- Need for specialized facilities and specific technical and scientific skills of manufacturing and testing personnel
- Technology transfer and showing comparability highly challenging – strong impact on global development
- Cost of therapies potentially quite high – at least initially

Evolving Regulatory Environment

Paradigm shift – emergence of expedited programs for promising medicines

- To address unmet medical needs for serious conditions
  - US FDA issues final Guidance for Expedited Programs for Serious Conditions – Drugs and Biologics (May 2014)
  - EU –Rollout of Adaptive Pathway Pilot Program (March 2014), and more recent discussions on new scheme to foster rapid development and accelerated assessment for innovative medicines with rollout in 2016 (?)
  - JP – Enacts new law, “Act on Safety of Regenerative Medicine” and amends existing “Pharmaceuticals Affairs Act” (Nov 2013)
- However in order to leverage expedited pathways where *“the product is the process”*
  - Considerable challenges exist on the technical, quality and manufacturing aspects of these complex and unique biologic products
  - Recognized requirements for product characterization, development of release specifications, potency assays, comparability protocols for process changes & technical transfers to new manufacturing facilities

Approvals of Gene & Cell products worldwide

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Harmonisation needed for ATMPs

- Continue/expand harmonisation within ICH region
  - GMPs
    - Manufacturing changes will be the norm for ATMPs
    - Speed of science is breath taking (e.g., Gene Editing)
    - Technology rapidly outpacing both industrial and regulatory sciences
    - While common standards apply globally,

    » Significant variability in the interpretation of those standards encountered across countries and regions
  - Divergent product classifications/definitions add to complexity in migrating through regulatory pathways on global level
    - E.g., device in one region, cell product in another region and transplant product in 3rd region
    - “351 product” in US, ATMP in EU, Regenerative Medicne Product in JPN
    - More-than-Minimal Manipulation/Substantial Manipulation/Complex Processing
    - GxP systems to apply
    - Different legislative systems
    - Heterogeneous regulatory filings to be submitted and interactions with different regulatory bodies

Harmonisation needed for ATMPs

- Ultimate goal – achieve harmonisation to a degree where a single registration dossier/package meets the market authorisation requirements across regions (MAA/BLA/JNDA)
  - Regulators are speaking to each other: Bi-monthly cluster meetings between EMA, FDA & Health Canada;
  - International Pharmaceutical Regulators Forum (IPRF) have specific groups on Cell & Gene Therapies (EMA, FDA, HC, TGA, KOR, PMDA) that meet regularly

Current state of ATMPs in Europe

Limited success to date

- Since implementation of ATMP Regulation (1394/2007) in December 2008[1]
  - 14 Market Auhorisation Applications filed leading to:
    - 6 positive opinions adopted corresponding to 5 authorised ATMPs
    - 3 negative draft opinions
    - 4 withdrawals during review &
    - 4 applications currently under review
  - Of the 5 authorised ATMPS
    - 1 has had its MA suspended due to closure of its manufacturing site due to commercial reasons[2]
    - 1 voluntarily requested withdrawal of its MA due to commercial reasons[3]
    - Remaining 3 have only achieved limited success in securing reimbursement

1. EMA CAT Monthly Report – Sep 2015: http://www.ema.europa.eu/docs/en_GB/document_library/Committee_meeting_report/2015/10/WC500194686.pdf
2. http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Maci_20/WC500173680.pdf
3. http://www.ema.europa.eu/docs/en_GB/document_library/Public_statement/2015/05/WC500186950.pdf

Current state of ATMPs in Europe

Plenty of reasons for hope

- Since implementation of ATMP Regulation (1394/2007) in December 2008
  - Research & Development of ATMPs in Europe remains strong
    - 145 requests for ATMP classification submitted >> leading to adoption of 136 classifications
    - 164 Scientific Advice procedures and 255 discussions
    - 41 Paediatric Investigation Plans for ATMPs discussed
    - 7 Quality & non-clinical certification requests for Small & Medium-Sized Enterprises received leading to 6 certifications
  - Relevant guidelines open for public comment with proposed provisions for flexibility, risk-based, and case-by-case considerations
    - Conditional Approval
    - Accelerated assessment
    - GMPs for ATMPs (EC)
  - Adaptive Pathway Pilot Programme

EMA CAT Monthly Report – Sep 2015:
http://www.ema.europa.eu/docs/en_GB/document_library/Committee_meeting_report/2015/10/WC500194686.pdf

Hurdles to overcome for ATMP patient access

Importance of parallel Scientific Advice & HTA consultation

- Current health eco-systems
  - Are not set up to deliver such complex therapies
  - Will undervalue ATMPs, reducing incentives to develop and market them
  - Not set up to properly fund ATMPs, thus limiting access to few or no patients
- Payers yet to implement cost/benefit models for curative approaches and one-off treatments with potential life-long efficacy
- Uncertainty on length of clinical outcome measures required for reimbursement
- Many targets are orphan indications with uncertainties regarding reimbursement in many regions
- Know natural history of disease trying to treat
- Consult with patients & KOLs when designing clinical trials
- Engage both Health Authorities and HTA's when seeking Scientific Advice
- Market sequencing and entry highly challenging

Clinical trial authorisation for ATMPs

More flexibility especially in the timelines of response to HAs

- CTA process for ATMPs can be challenging for sponsors
  - Different levels of experience across Member States (MS)
  - High number of detailed & complex questions often poses challenges to meet short response timeframes (≤10 days under VHP) which may lead to automatic withdrawal and re-submission
  - CTR No 536/2014: For ATMPs, although the review timelines might be extended by 50 days for MSs for expert consultation, the regulation doesn't foresee an extension of the 12-day response time
- Many ATMPs are also considered GMOs
  - Classification of ATMPs at national level → unclear delineation between transplantation/transfusion and ATMPs?
  - No harmonization between MS: multicentre clinical studies are a complicated undertaking
- Manufacturing licences for product manipulations with different requirements across MS

Other challenges

- Hospital Exemption
  - There is a need & place for HE
  - HE should be uniformly implemented across Member States
  - Should be revoked when ATMP approved to treat same condition
- Definition of Similarity
  - Regulatory exclusivity and patent protection, traditionally based on the concept of *sameness* in molecular structure, mechanism and therapeutic indication (small molecules)
  - With well-characterized biologics, the concept of “sameness” morphed into multi-dimensional concept of *similarity*
    - Equivalence based on structural analysis, manufacturing process and therapeutic target.
  - For ATMPs complexity in defining criteria for similarity or sameness are even more challenging.
    - Will each entity be considered unique, or is there a standard way that these definitions will be applied to ATMPs?
    - What criteria will be applied when determining if a similar ATMP has demonstrated significant benefit over existing authorised ATMP holding Orphan Drug Exclusivity?

Conclusion

- ATMPs have the potential to improve the lives of patients suffering from serious conditions where unmet medical needs exist
- However, considerable challenges remain before their widespread use and access becomes a common reality
- It is our desire to work with all stakeholders in a transparent manner to bring these transformative therapies to patients in a safe but expedited manner
- Novartis wishes to thank EMA & EuropaBio for this opportunity to speak at today's Information Day