CHANGING PROMISES INTO REALITY

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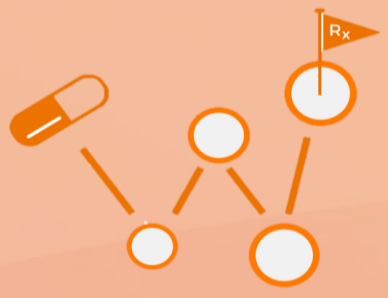
SUCCESFULLY TRANSITIONING GENE-THERAPY PRODUCTS FROM LAB TO INDUSTRIAL ENVIRONMENT



An essential part is the transition from the lab-table environment to the industrial environment This transition is based on:

- Defining a process & product
- Embed robustness into process and product quality
- Meeting external expectations (authorities)
- Multidisciplenary cooperation

LARGE DIVERSITY GENE TECHNOLOGY AREA

Technology area	Technology
Gene Delivery	• Viral vectors • Non-viral vectors (lipids/liposomes; polymers, nanoparticles) plasmid DNA
Gene Expression regulation	• siRNA and miRNA • Antisense Oligonucleotides
Genome / epigenome editing	• Engineered nuclease (CRISPR/Cas 9, TALENS, ZNF)

Examples of approved gene therapy products:

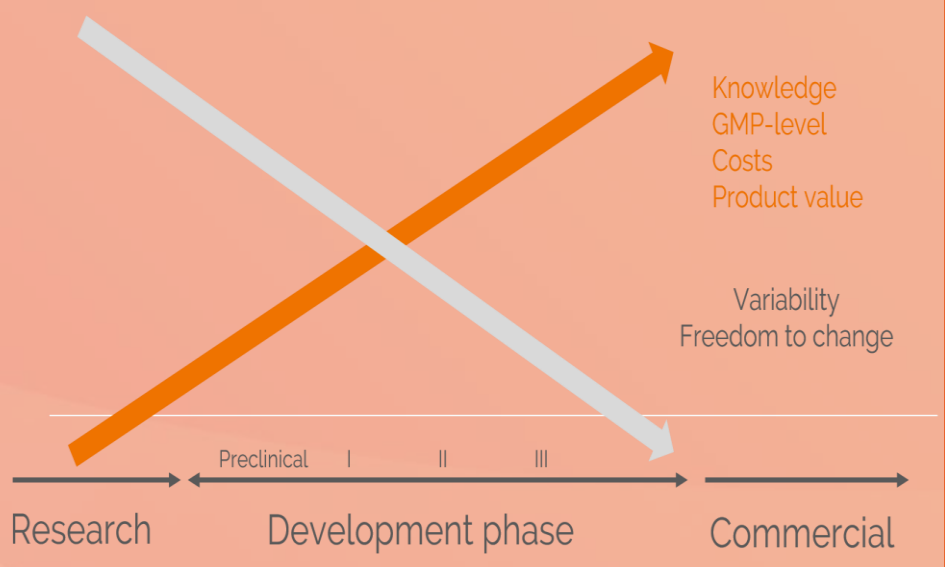
Glybera, AAV (LPLD)
Approved 2012

Imlygic, Herpes simplex (Melanoma)
Approved 2015

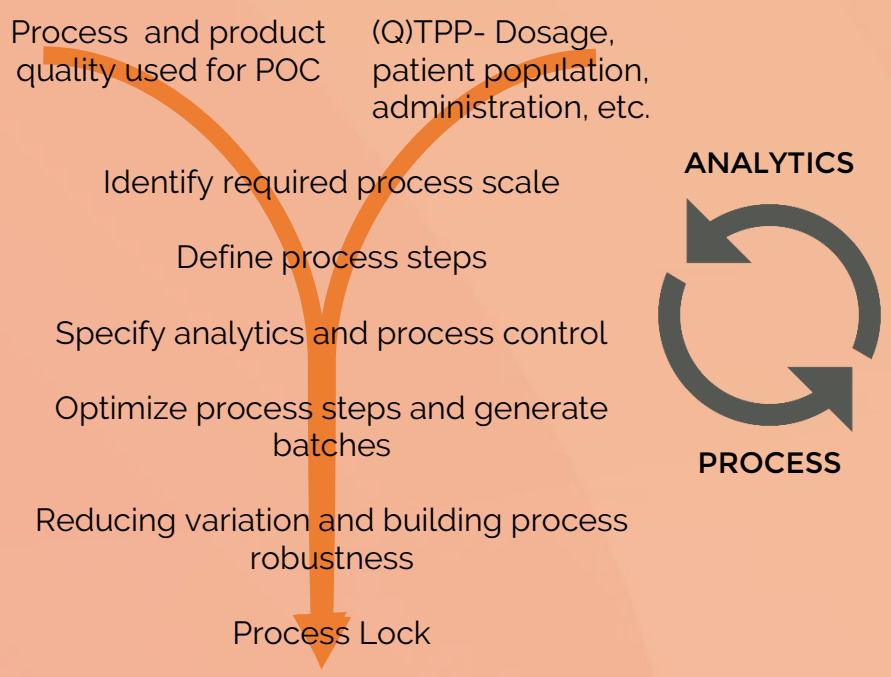
Strimvelis, ex-vivo retroviral vector (Immunodeficiency)
Approved 2016

Zalmoxis, ex-vivo retroviral vector (Cancer, stem cell transplantation)
Approved 2016

BASIC PRODUCT DEVELOPMENT



CMC PROCESS DEVELOPMENT



CMC ANALYTICS

Gene therapy products are complex. An analytical package should be capable to:

- demonstrate consistency (lot to lot)
- assess the suitability of the product for its intended use.

Basic testing programm (ICH Q6B):

Biological activity (potency, infectivity)	Identiy (DNA, protein)	Impurities (process&product related)
Content (GC, protein&DNA composition, total particles, total protein)		
Contaminants (endotoxin, sterility)	Purity (ratio tp/gc)	Physicochemical (pH, osm, extract. vol.)

CMC FOCUS THROUGHOUT DEVELOPMENT

- To develop a gene-therapy product, an integrated CMC focus is required.
- Integration of multidisciplinary teams and agreement on the target product profile is essential for successful development of a gene-therapy product .
- Changing a process&product from limited specified to defined requires an iterative approach.
- Knowledge drives this iterative approach.
- External expectations are outlined in guidelines.
- Understanding internal and external expectations should be part of an integrated CMC focus.