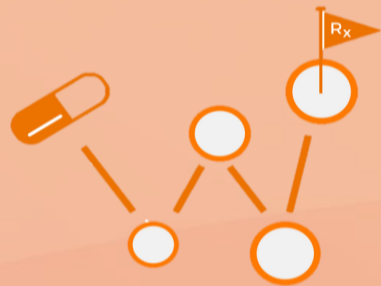


## SUCCESSFULLY TRANSITIONING GENE-THERAPY PRODUCTS FROM LAB TO INDUSTRIAL ENVIRONMENT



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)
- Multidisciplinary cooperation

## LARGE DIVERSITY GENE TECHNOLOGY AREA



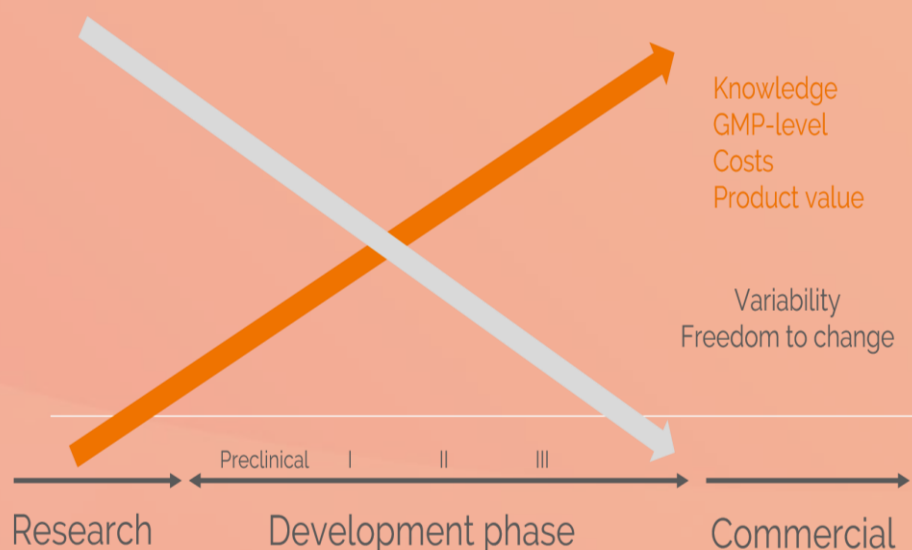
Technology area	Technology
Gene Delivery	<ul style="list-style-type: none"> <li>• Viral vectors</li> <li>• Non-viral vectors (lipids/liposomes; polymers, nanoparticles) plasmid DNA</li> </ul>
Gene Expression regulation	<ul style="list-style-type: none"> <li>• siRNA and miRNA</li> <li>• Antisense Oligonucleotides</li> </ul>
Genome / epigenome editing	<ul style="list-style-type: none"> <li>• Engineered nuclease (CRISPR/Cas 9, TALENS, ZNF)</li> </ul>

### Examples of approved gene therapy products:

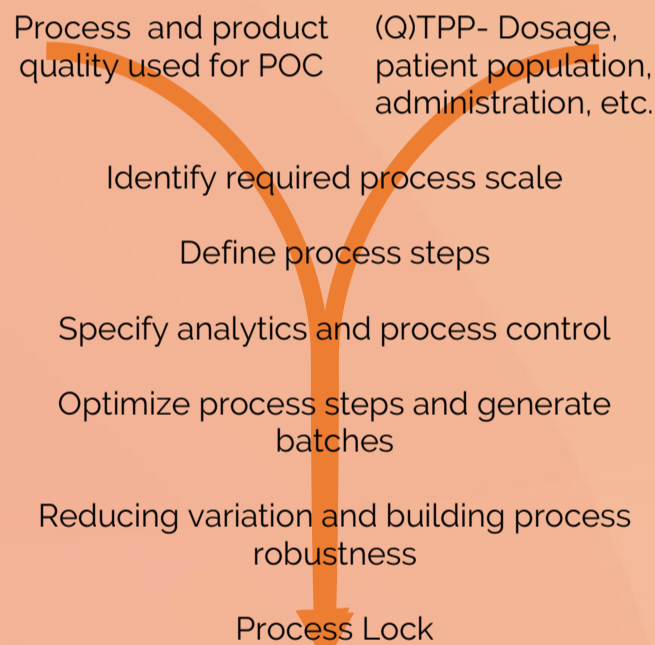
- |   |  |
|---|--|
| Glybera, AAV (LPLD)<br>Approved 2012                                      | Imlygic, Herpes simplex (Melanoma)<br>Approved 2015                                      |
| Strimvelis, ex-vivo retroviral vector (Immunodeficiency)<br>Approved 2016 | Zalmoxis, ex-vivo retroviral vector (Cancer, stem cell transplantation)<br>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 program (ICH Q6B):

Biological activity (potency, infectivity)	Identify (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.