“Regulatory lessons from the approval of COVID19 vaccines relevant to gene therapy products”
Content of this talk:

- My background with Medicinal products and gene therapy in particular
- Legal definitions of Gene therapy products vs other gene delivery products
  - History, examples, consequences of classification, sources for your product classification
- GMO, brief overview.
- The market approval of COVID-19 vaccines
  - Overview of Medical product development
  - Regulatory tools for enhancing evaluations of product to meet an emergent need
  - Analysis of steps taken to evaluate 4 gene delivery vaccines in the light of limited data on the product
- Other actualities (e.g. Ph. Eur. new general monograph and updating of general text on GTMP)
My background in regulatory sciences

- 2002-2017 the Swedish Medical Products Agency as a quality and non-clinical expert evaluating biologic medicinal products for:
  - Clinical trial applications (CTA)
  - Marketing applications (MAA) for EMA
  - Scientific advice, EU and national scientific advice

  - Writing guidelines on gene therapy products
  - Drafting Annex I, part IV (advanced therapy products) of medical directive (2001/83)
  - Updating the legal definition of GTMP

- Member of Gene Therapy Products Working Party EDQM (present):
  - Drafting Ph. Eur. general chapter on gene transfer products 5.14
  - Updating the text on Gene Therapy Products (ongoing)

- ProPharma Group Principal Consultant (2017-2021):
  - Expert consultation on Quality and Non-clinical matters working with SME and big pharma developing biological products

- Independent consultant on biological products (present)
Part I

Legal definitions of Gene therapy products vs other gene delivery products
Legal web of definitions for human Medicinal Products (EU)

The hierarchy:

▶ Medicinal product: Article 1(2) of Directive 2001/83/EC - i.e not veterinarian MP, not MD.

▶ Biologic Medicinal Product: Part I of Annex to Directive 2001/83/EC. Including also: immunological products, blood & plasma products and ATMP. Excluding ”small molecules” and molecules not from a biological source

▶ ATMP : Article 2(1) of Regulation (EC) No 1394/2007. Including GTMP, sCTMP and TEP.

▶ GTMP: Part IV of Annex to Directive 2001/83/EC. Excluding vaccines
The current legal definition of GTMP

2.1. Gene therapy medicinal product

Gene therapy medicinal product means a biological medicinal product which has the following characteristics:

- (a) it contains an active substance which contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence;

- (b) its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence.

Gene therapy medicinal products shall not include vaccines against infectious diseases.
Examples of products containing added genes or parts there of but not a GTMP...

- Cells modified with a marker gene (Zalmoxis) - Contain a non-therapeutic gene
- Exon skipping or antisense synthetic oligonucleotides - Not biological source, not recombinant
- Plasminogen activating purified genomic DNA? - Not recombinant DNA (never considered as a GTMP)
- Nanoparticles polymer containing the gene editing components (CRISPR/Cas9 and the single guide RNAs) - No recombinant DNA
- Allogeneic, Genetically modified (E4ORF1) human umbilical cord endothelial cells - Contain a non-therapeutic gene
Resources for classification on the EMA website

Scientific recommendations on classification of advanced therapy medicinal products

The European Medicines Agency's (EMA) Committee for Advanced Therapies (CAT) delivers scientific recommendations on whether a medicine can be classified as an advanced therapy medicinal product (ATMP).

Update: The list of medicines that the CAT has assessed and recommended classifying as ATMPs or not since March 2019 is available below. EMA updates the list on a quarterly basis.

ATMP classifications granted before March 2019 are available separately in the archive below.

### Scientific recommendations on classification of advanced therapy medicinal products (XLSX/104.52 KB) (updated)

First published: 19/04/2021  
Last updated: 27/10/2021  
EMA/140033/2021

<table>
<thead>
<tr>
<th>Product description</th>
<th>Therapeutic area</th>
<th>Classification</th>
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GTMP or not, does it matter?

- ATMP has specific provision during development (e.g. Scientific advice imbursements for SME, extended time lines for CTA)
- Classification assures that applications runs through relevant committees (e.g. CAT).
- Specific recommendations/provisions for GTMPs in the guidelines and in Ph. Eur.

Key is whether your product is a medical product or not
GMO legislation

Definition GMO (Directive 2001/18/EC):

- An organism, with the exception of human beings, in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination.
- Organism means any biological entity capable of replication or of transferring genetic material
GMO legislation...

- Independent from Medical legislation, e.g. a product can be GMO but not GTMP and vice versa

- Focus is how does your product affect the environment?
  - Depends on:
    - Product characteristics (e.g. replicative capacity, properties of the inserted gene..)
    - Releasing environment (exposure and sensitivity)

- Evaluated by an Environment Risk Assessment - ERA
  - For CTA assessment is made national. For MAA assessment is made by a lead authority

- Harmonised common application form available for some products in CT (e.g. GM cells, AAV)

- Specific legislation made for COVID-19 trials (REGULATION (EU) 2020/1043)
Part II

The market approval of COVID-19 vaccines - Analysis
Overview of medicinal product development

Clinical development:
- Pre-clinical proof of principle
  - Phase I
  - Phase II

Proof of concept = Marketing license
- Phase III (pivotal)

Quality (CMC) development:
- Identify & establish
  - control of quality attributes
  - qualification of process variables

Complexity
Flexibility
Overview of medicinal product development...

At the stage of marketing authorization application:

- The quality of a medicinal product should be appropriate with a purpose to:
  - Assure that the established clinical profile (E/S) is not influenced by variable quality when put on the market.
    - Specifications within qualified limits
    - Process validation to verify consistent quality on the market (within qualified limits)

  → Confidence with the established clinical profile
EMA, available options to speed up the regulatory process to meet an emergent need

- **Rolling review procedure:**
  - Early interaction with EMA
  - B/R evaluated as data becomes available to decide if the benefits outweigh the risks.
  - Continues until enough evidence is available for a formal MAA.

- **Conditional marketing authorisation:**
  - A positive B/R balance
  - Likelihood to provide comprehensive data post-authorisation
  - Unmet medical need (including emergent need)
  - The MAH must fulfil specific obligations (SO) within defined timelines post approval.

- **Concurrent process validation:**
  - Only for exceptional circumstances
  - The validation protocol is executed concurrently with commercialization of the validation batches.
The MAA evaluation of 4 gene delivery based vaccines

- Comirnaty: active substance = Recombinant mRNA
- Spikevax: active substance = Recombinant mRNA
- Vaxzevria: active substance = Recombinant chimp Adenovirus (ChAdOx1)
- COVID-19 Vaccine Janssen: active substance = Recombinant human Adenovirus (serotype 26)
Overview of Specific obligations (SO)

- **Quality:**
  - Process validation of commercial manufacture
    - All: submit data on process validation post approval (PA)
  - Comparability between clinical batches and commercial batches
    - All: additional comparability data needed (PA)
  - Stability data provided as updated (std procedure for MA)
  - Specific stability related (transport, in use, general storage conditions, leachables, light sensitivity)
    - REC (Cominarty; Vaxzervria, Jansen)
  - Specification. Review limits PA (all) SO
    - Uncertainty over qualified limits (e.g. potency Vaxzervria); Process related substances/impurities (mRNA vaccines)
  - Quality of excipients
    - Comirnaty; Spikevax

- **Non-clinical**
  - Limited SO due to vast amount of clinical data
  - Information on kinetics (i.e. biodistribution data Vaxzervria ongoing (REC)
Conclusions on approval of Covid-19 vaccines

- A massive effort by industry, moving from idea to clinical evaluation
- And managing manufacture & distribution of products on a global scale
- Regulatory system has shown procedures that are adapted to the emergent need while still ensuring efficacy & safety of products on the market
- Firm conclusions on feasibility of the approaches used need to be evaluated as more experiences is gained, but so far quite good.
- The concept of using gene based approach to rapidly develop effective medicines has been further realised.
- Medicines is all about benefit/risks and the balance for gene based medicines has now weighted over towards the beneficial side.
Part III

Other regulatory activities in the area of GTMP: Updating the Ph. Eur. general chapter 5.14, Gene transfer medicinal products for human use
Proposals for updating the general texts in 5.14

- Product types that are represented on the market will be included in a general monograph (3186):
  - GENETICALLY MODIFIED HUMAN AUTOLOGOUS CELLS
  - ADENO-ASSOCIATED-VIRUS VECTORS
  - RECOMBINANT ONCOlytic HERPEX SIMPLEX VIRUS
  - Section on GENERAL REQUIREMENTS

- Product types that are not on the market will be included in a new general text (5.32):
  - PLASMID VECTORS
  - BACTERIAL CELLS FOR THE MANUFACTURE OF PLASMID VECTORS
  - GENETICALLY MODIFIED BACTERIAL CELLS
  - ADENOVIRUS VECTORS
  - POXVIRUS VECTORS
  - RETROVIRIDAE-DERIVED VECTORS
(TACK = Thank you in swedish)
Questions?
&
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