“Regulatory lessons from the approval of COVID19 vaccines relevant to gene therapy products”

ATMP Sweden 2021

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
- EMA CHMP Gene Therapy Working Party, core member (2005-2012):
  - 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

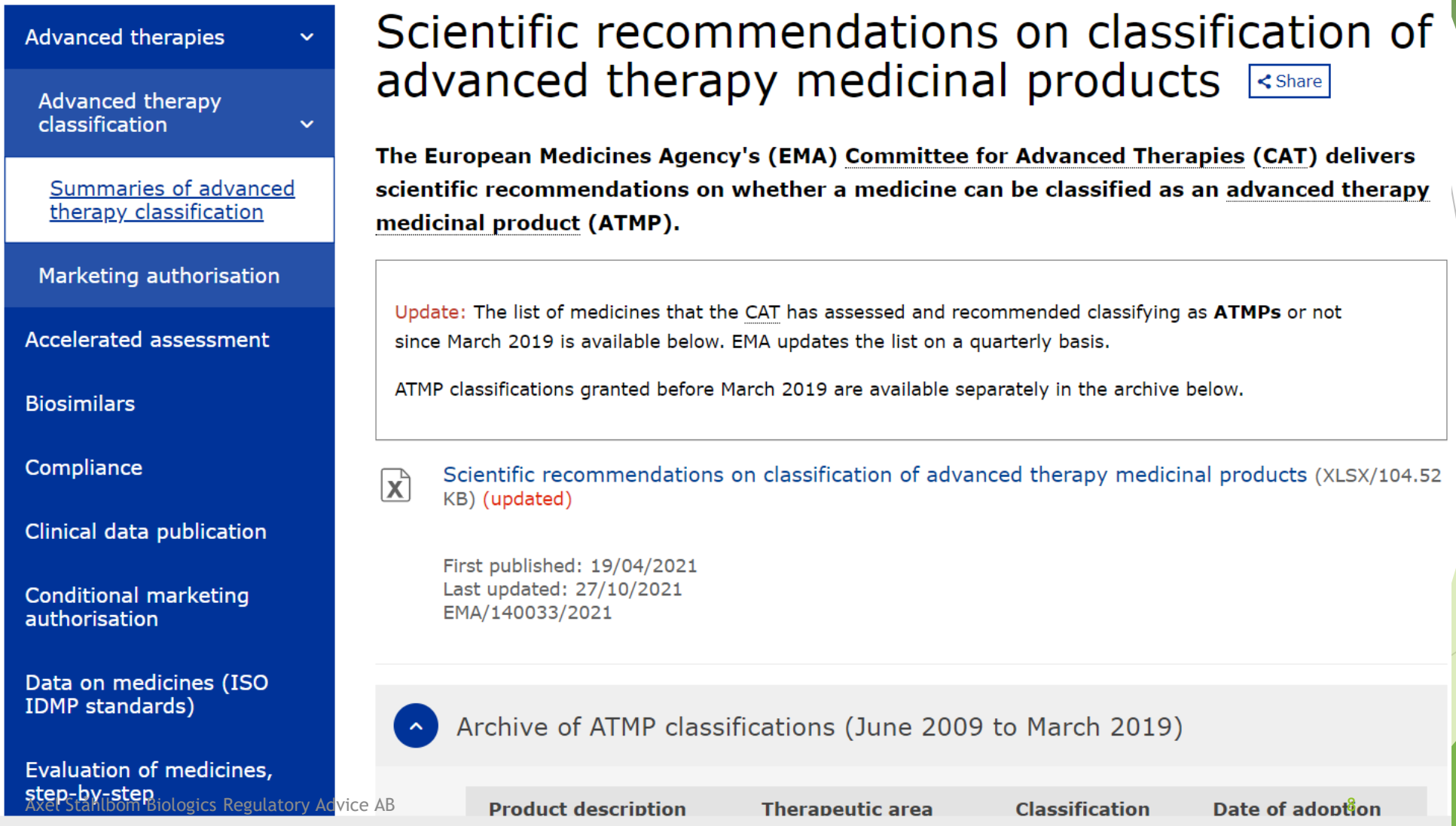
The current legal definition of GTMP

- 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



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…

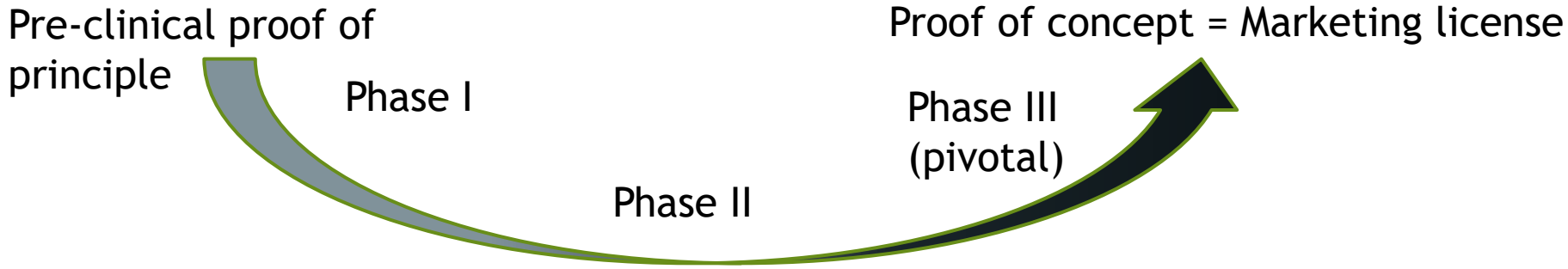
- Independent from Medical legislation, e.g. a product can be GMO but not GTMP and vice versa
- Focus is how does your product affect the environment?
  - Depends on:
    - Product characteristics (e.g replicative capacity, properties of the inserted gene..)
    - Releasing environment (exposure and 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

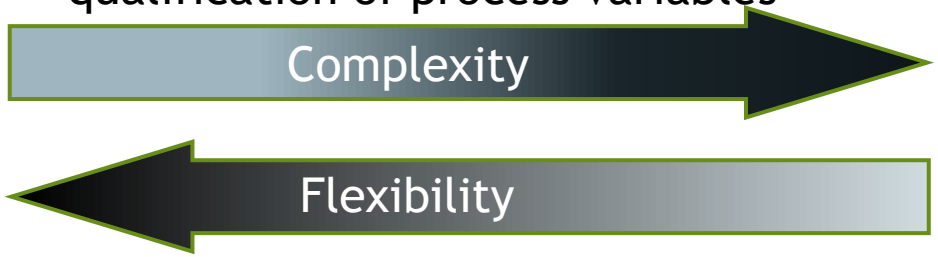
Clinical development:



Quality (CMC) development:

Identify & establish

- control of quality attributes
- qualification of process variables



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 Vaxzevria); 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 Vaxzevria 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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