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mRNA Vaccines

an EU Regulator's Perspective

CASSS Symposium on mRNA
May 29 to 30, 2025

Petra Schlick

AGES/Division Austrian Medicines and Medical Devices Agency

Disclaimer

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- The views and opinions expressed in the following presentation are those of the speaker and do not necessarily reflect the view of the AGES/BASG and/or the EMA

Agenda

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- Introduction
- EU regulatory experience with mRNA vaccines
- New guidance for mRNA vaccines
  - three new chapters in the European Pharmacopoeia (Ph. Eur.)
  - EMA's new draft guideline on quality aspects of mRNA vaccines
- Additional regulatory considerations, covered in EMA GL

Austrian Agency for Health and Food Safety (AGES)

Austrian Medicines & Medical Devices Agency

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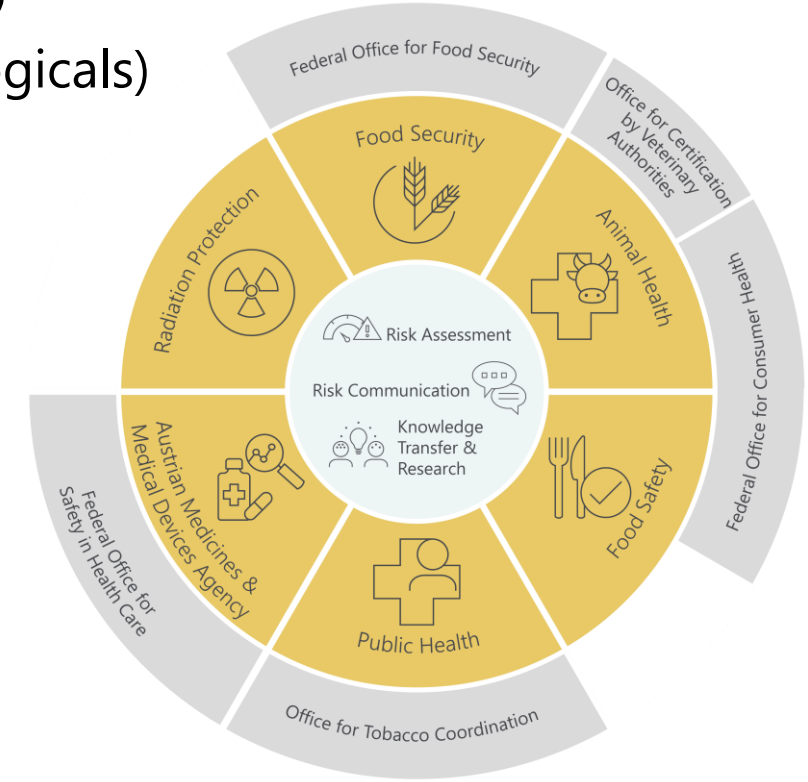
AGES

- Austrian Medicines & Medical Devices Agency (MEA)
  - Division of AGES
  - Resources for Federal Office for Safety in Health Care (BASG)
  - All product types (human, veterinary, chemical entities, biologicals)
  - At all stages of lifecycle
    - Scientific advice
    - Clinical study authorisation
    - Marketing authorisation
    - OMCL release
    - Inspection
    - Pharmacovigilance
    - Market monitoring



Austrian Agency for Health and Food Safety (AGES)

Austrian Agency for Health and Food Safety

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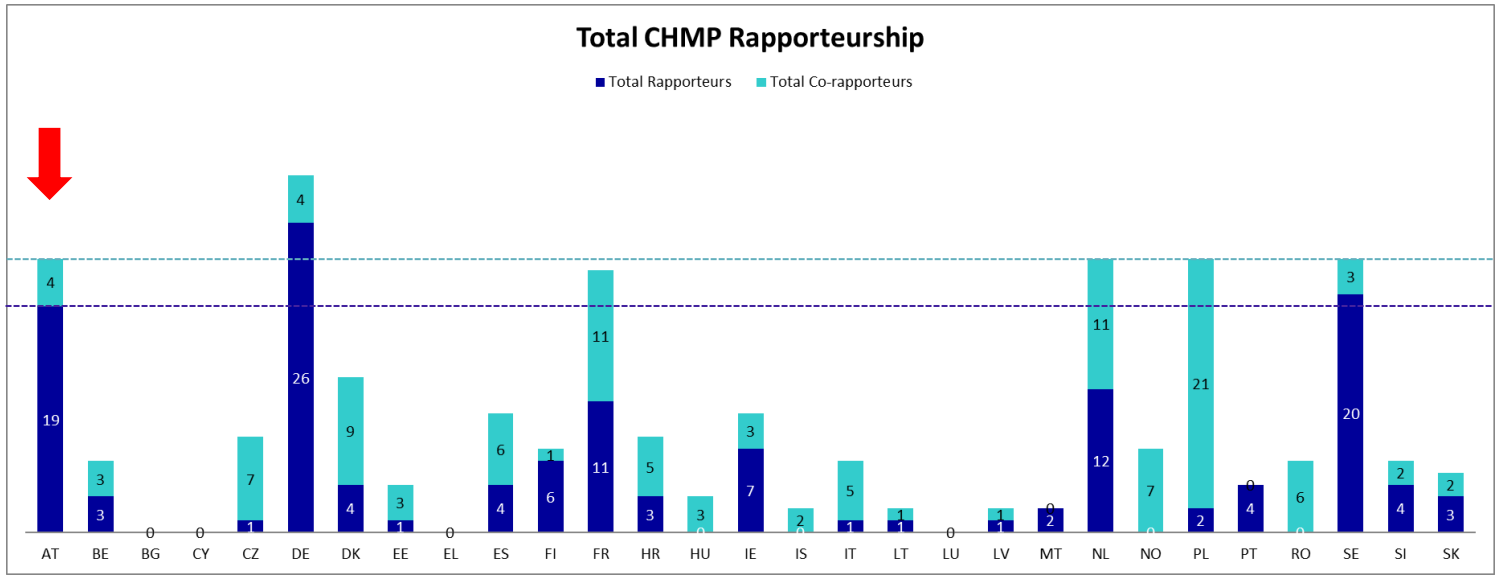
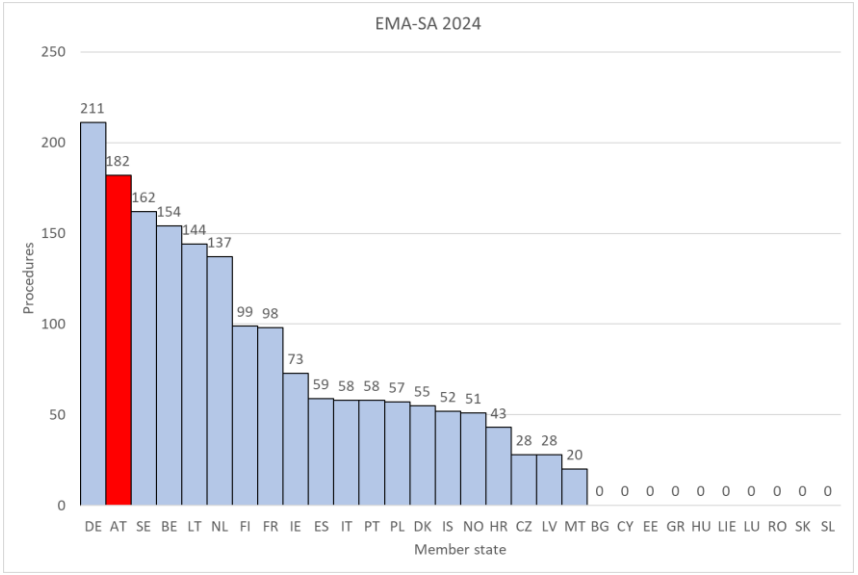
AGES

- One of the leading agencies in EEA
  - Members in EMA committees/Working parties/Expert groups/EDQM
  - Significant contribution to assessment and guidance





Marketing Authorization

Excellent collaboration within the European Network

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- mRNA vaccines approved by EMA

Product	MAH	Indication	Approved
Comirnaty + strain updates	BioNTech	COVID-19	12/2020
Spikevax + strain updates	Moderna	COVID-19	01/2021
mRESVIA	Moderna	RSV	06/2024
Kostaive	Arcturus	COVID-19	12/2024

- Additional **Marketing Authorization Applications** currently under review
- multiple **Scientific Advices** received, future pipeline of MAAs expected

Common Topics & Assessment Issues

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Scientific advice procedures

- Starting materials
- Comparability clinical/commercial lots
- Definition of active substance / intermediate / finished product
- Process validation approaches (PPQ)
- Platform technology
- Potency testing
- Stability
- Variant strain updates

Marketing authorization applications

- Characterisation
- Comparability
- Novel excipients
- Process validation (PPQ)
- Specifications
- Analytical methods
- Potency testing
- Stability

New Regulatory Guidance - EDQM

EPC adopted three new general texts in Ph. Eur.

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- At its 180th session in November 2024, the European Pharmacopoeia Commission (EPC) adopted three new general texts namely:

  - **mRNA vaccines for human use** (**5.36**), covering mRNA packaged in lipid nanoparticles, i.e. mRNA-LNP medicinal products

  - **mRNA substances for the production of mRNA vaccines for human use** (**5.39**), covering mRNA active substances used in the manufacture of mRNA vaccines

  - **DNA templates for the preparation of mRNA substances** (**5.40**), covering the linear DNA template used as starting material for the preparation of mRNA substances

New Regulatory Guidance - EMA

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EMA released new draft GL on the quality aspects of mRNA vaccines

- The guideline addresses
  - **specific CMC aspects** relevant for **mRNA vaccines against infectious diseases** and provides definitions for starting materials, active substance, and finished product.
  - **Additional considerations:** changes in existing vaccine strains, bivalent and multivalent vaccines, self-amplifying mRNA vaccines, other delivery systems and use of platform technology/prior knowledge
- **Out of scope** are other mRNA-based medicinal products & mRNA vaccines in clinical trials. However, certain scientific principles may also be applicable to those.
- Next steps:
  - 6-month public consultation **(Apr-Oct 2025)**
  - Anticipated publication of final guideline **(2026)**

We are looking forward to your comments!

EMA NEW DRAFT GUIDELINE

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Table of contents

- Follows eCTD structure
- Guidance specific to mRNA vaccines against infectious disease
- General requirements not specific to mRNA vaccines are not addressed

KEY MESSAGES – Definitions

Glossary

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- **Starting Material:**
  - Linear DNA template, characterized in line with Ph. Eur. 5.40 *DNA templates for the preparation of mRNA substances*
- **Active Substance:**
  - mRNA, as defined in Ph. Eur. 5.39 *mRNA substances for the production of mRNA vaccines*
- **Finished Product Intermediates:**
  - e.g lipid mixtures, mRNA mixtures, lipid-mRNA mixtures
- **Finished Product:**
  - preparations containing mRNA molecules capable of inducing a specific and active immunity in humans, Ph. Eur. 5.36 *mRNA vaccines for human use*
  - a suitable delivery system is required

KEY MESSAGES – Manufacture

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Control of materials, process characterisation & validation

- **Control of materials**
  - Linear DNA template is considered as critical starting material, hence, a detailed description of its manufacture and thorough characterization is expected

- **Process characterization** and **process validation**
  - Acceptable operational range for various processing parameters
  - Critical processing steps and their acceptance criteria
  - Adequate removal of product- and process-related impurities
  - Reusability of purification components
  - Any in-process hold times proposed
  - Consistency of the production process on an appropriate number of batches

KEY MESSAGES – Characterisation

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Characterisation studies inform specifications' setting

- Characterisation studies of active substance and final product should be
  - performed **throughout development** → comparability
  - including clinical batches to inform specifications setting
  - using state of the art methods
  - on both active substance and finished product
  - a **Quality Target Product Profile** (QTPP) should be defined

- Relevant **quality attributes** include, but are not limited to
  - primary and higher order structure
  - mRNA integrity and purity
  - impurities (process- and product-related)
  - ability to be translated into the correct protein
  - FP: particle size and size distribution, encapsulation efficiency etc.

KEY MESSAGES - Specifications

Expectations are harmonized between Ph. Eur. texts and EMA draft GL

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- **Active Substance**
  - Identity
  - Appearance, pH
  - 5‘ cap & 3‘ poly(A)tail
  - residual DNA template
  - residual dsRNA
  - residual protein
  - bacterial endotoxins & bioburden
  - residual solvents/reagents/ other process-related impurities
  - mRNA content
  - mRNA integrity

- **Finished Product**
  - Identity
  - Appearance, pH, osmolality, extract. vol.
  - particulate contam.: sub-visible particles
  - LNP size and polydispersity
  - Individual lipids identity and content
  - Product- and process-related impurities
  - Bacterial endotoxins & sterility
  - mRNA content
  - mRNA encapsulation efficiency
  - mRNA integrity
  - Cell-based *in vitro* expression assay

POTENCY

KEY MESSAGES - Stability

General considerations in line with ICH Q5C and ICH Q1 guidance

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- **Shelf-life claim** is based on long-term, real-time and real-condition studies
- Supportive data from batches **representative of commercial material**
- Shelf life is supported with **consecutive stability studies** reflecting all intermediate storage conditions
- **Extrapolation of shelf-life and storage conditions** could be considered, dependent on prior knowledge

- ICH stability guidelines under revision

17 April 2025

ICH Q1 Draft Guideline & Step 2 Presentation Now Available on the ICH Website

The ICH Q1 draft Guideline on "Stability Testing of Drug Substances and Drug Products" reached Step 2b of the ICH Process on 11 April 2025 and entered the public consultation period.

Additional Regulatory Considerations

Changes in existing mRNA vaccine strains

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- Key messages to consider
  - only **changes related to the new strains** used may be introduced.
  - the **potential need of non-clinical and/or clinical data** to support a strain update procedure cannot be excluded.

- General expectations as regards **dossier content**:
  - detailed control of materials/characterization of new strains
  - changes to the manufacturing process and specifications require justification
  - details on method updates and re-validation of strain-specific methods
  - comparability analysis of historical and new strain(s)
  - process validation: three active substance and three finished product PPQ batches
  - stability data are required for both the active substance and finished product

Additional Regulatory Considerations

Prior knowledge & platform technologies

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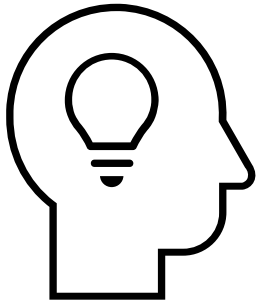
- Prior knowledge refers to existing knowledge and includes **internal knowledge** (e.g., development and manufacturing experience), **external knowledge** (e.g., scientific and technical publications, including vendors' data, literature, and peer-reviewed publications), or the application of established scientific principles (e.g., chemistry, physics, and engineering principles).



Additional Regulatory Considerations

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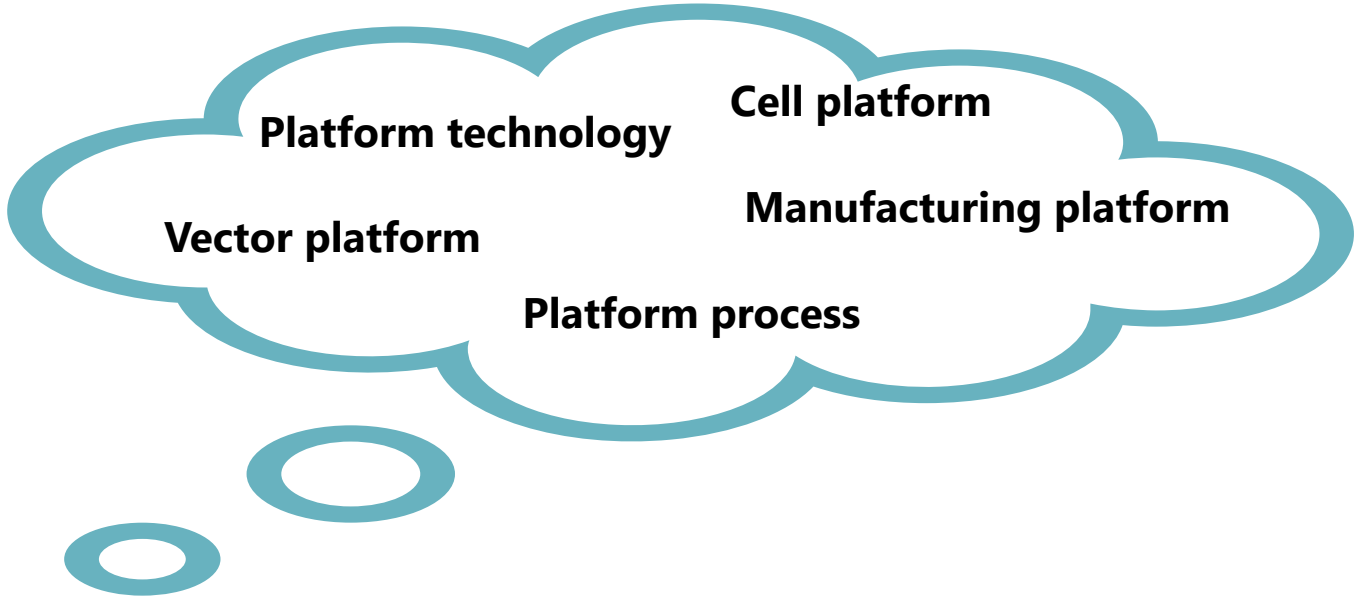
What is a platform?

ICH Q11 platform definition: The approach of developing a production strategy for a new drug starting from manufacturing processes **similar** to those used by the same applicant to manufacture other drugs of the same type (e.g., as in the production of mAbs using predefined host cell, cell culture, and purification processes for which **considerable experience** already exists).

Different perceptions of Platform manufacturing & Considerable experience



Additional Regulatory Considerations

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Use of prior knowledge is well accepted

- Prior knowledge gained from previous developments can be used, however, a **product-specific dossier** is still required to support a new MAA.

- **Prior knowledge** can be used to support e.g.
  - Process development and/or validation studies
  - Method validation
  - Container closure systems
  - Shelf-life claims

Case-by-case

- Acceptability depends on e.g. number of (representative) licensed or developed products, in-depth understanding of product-specific vs product-agnostic parameters, conclusive risk-assessments, etc.

Additional Regulatory Considerations

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Bivalent and multivalent vaccines

- Composition/content of each variant/strain needs to be specified
- Pharmaceutical development needs to be described in detail
- Mixing studies and additional characterization data (homogeneity)
- Suitable identity and the cell-based functionality test to discriminate all antigens included in the vaccines and determine their respective ratio

Self-amplifying mRNA vaccines

- Minimal requirements are essentially the same as for non-amplifying mRNAs
- Characterisation studies to demonstrate that both the replicase and the antigen are correctly expressed and functional

TAKE HOME MESSAGES

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- **New guidance documents** are available with the aim of supporting developers, manufacturers, regulatory agencies and national control laboratories

- EMA provides additional **support to developers** via e.g.
  - Scientific Advice
  - Innovation Task Force (ITF)
  - Business pipeline meetings (BPM)
  - Portfolio and technology meetings
  - PRIME scheme
  - Emergency Task Force (ETF)

- **Scientific advice** is also provided by NCAs

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Austrian
Federal Office for
Safety in Health Care
BASG

Petra Schlick

Senior Quality Assessor

BASG -
Austrian Federal Office for Safety in Health Care

Traisengasse 5
1200 Vienna
T +43 (0) 50 555-36668

petra.schlick@ages.at
www.basg.gv.at