EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

12 October 2023
EMA/CHMP/453561/2023
Committee for medicinal products for human use (CHMP)

Concept paper on the revision of the Non-clinical and Clinical Module of the influenza vaccines guideline

Agreed by Vaccine Working Party	June 2023
Agreed by ETF	July 2023
Adopted by CHMP for release for consultation	12 October 2023
Start of public consultation	1 November 2023
End of public consultation	30 January 2024

The proposed guideline will replace Guideline on influenza vaccines, non-clinical and clinical modules (EMA/CHMP/VWP/457259/2014).

Comments should be provided using this EUSurvey form. For any technical issues, please contact the EUSurvey Support.

Keywords	Vaccine platforms, mRNA, immunobridging, effectiveness, influenza, pandemic influenza, zoonotic vaccine, regulatory requirements

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1. Introduction

The current influenza vaccines guideline covering non-clinical and clinical modules (EMA/CHMP/VWP/457259/2014) was adopted in July 2016. Developments in the field of influenza vaccines and experience with applications for scientific advice and for marketing authorisation since 2016 have pointed to the need for additions to and revisions of the current text.

2. Problem statement

Since the preparation and adoption of the current guideline text, the vaccine development landscape has changed, not least following the COVID-19 pandemic during which mRNA vaccines were introduced on a very large scale and are now being developed also against influenza. The current guideline text does not address mRNA vaccines, for which there are some additional considerations to mention, or influenza vaccines based on other novel platforms. Moreover, there have been several new seasonal influenza vaccines approved in the EU since 2016 as well as several requests for CHMP scientific advice that have highlighted issues that are not covered in the existing text or which require revision or clarification (e.g. requirements for updating influenza strains in zoonotic vaccines).

An important change since adoption of the current text has been the gradual replacement of trivalent seasonal influenza vaccines with quadrivalent vaccines incorporating two influenza A and two influenza B strains. The review of the clinical data in applications for some of these quadrivalent vaccines had raised issues that should be addressed in the updated text, including requirements for data in specific age sub-groups and the most appropriate comparator vaccines.

Work continues on assays relevant to determining immune responses to influenza vaccines. The current recommendations regarding serological studies may require updating accordingly.

Data reported from efficacy studies since 2016 have pointed to some matters that should be addressed when planning the studies and analysing the results. Furthermore, vaccine efficacy data that have been reported from some trials in some paediatric age sub-groups indicate the need to rediscuss the current recommendations for paediatric development programmes.

There has been an expansion in the use of human challenge studies in the early phases of influenza vaccine development. The current text does not address the possible role of such studies for purposes of proof of concept and dose finding.

In the last decade, there have been discussions on the possible role of neuraminidase (NA) in eliciting immune responses that may contribute to protection although not all influenza vaccines contain any NA and there is no control over the amount of NA in those that do. There is a need to acknowledge the uncertainties and, for those vaccines where the sponsor proposes to include NA (or mRNA encoding for NA), to provide some guidance on this.

The current guideline text addresses collection of vaccine effectiveness data for approved vaccines by season. The collection of reliable data, especially brand-specific data, has proven difficult even within countries with high quality influenza disease surveillance. There is a need to rediscuss the feasibility of the current recommendations, while still acknowledging the utility of such data to detect unexpected effectiveness signals.

Overall, there is some degree of urgency to revise the guideline on non-clinical and clinical development of influenza vaccines. In particular, to add sections relevant to the development of

mRNA-based influenza vaccines and to reflect on how lessons learned from the COVID-19 pandemic could be relevant to the development of influenza vaccines, including those intended only for pandemic usage.

3. Discussion (on the problem statement)

The following elements of the current GL need to be revised or added:

- Guidance on novel platforms under development for influenza such as the mRNA vaccine platform;
- Requirements for changing the strain subtypes in zoonotic vaccines;
- Reflection on the potential role of NA in vaccines and the implications for development of vaccines in which sponsors aim to control and specify the NA content;
- Consideration of brand-specific and/or overall vaccine effectiveness data by influenza season;
- Consideration of the design and role of human challenge studies;
- Revisiting requirements for paediatric development of influenza vaccines;
- Revisiting the primary read-out in serological studies;
- Editorial and structural changes to streamline and improve readability
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4. Recommendation

The Vaccine Working Party and the ETF recommend revising the guideline on influenza vaccines, non-clinical and clinical modules, taking into account the issues identified above.

5. Proposed timetable

The timetable for the concept paper is the following:
Discussion at VWP: 29 June 2023
Discussion at ETF: July 2023
Adoption by CHMP: 12 October 2023
Released for public consultation: October 2023 – January 2024
Adoption and publication of the final version: February 2024

The timetable for the revision of the guideline is the following:
Discussion in VWP on: Q1 2024
Discussion in ETF on: Q2 2024
Expected date for adoption on: Q3/Q4 2024 followed by 6 months public consultation
Expected finalisation: 2025

Resource requirements for preparation

An estimate of 2-4 VWP members will be required to draft the updated GL.

6. Impact assessment (anticipated)

The revised guideline will address some aspects of the non-clinical and clinical development of new influenza vaccine that are not covered by the current version. This will guide applicants of innovative

influenza vaccines through their product development to licensure and the revised version will also address post-approval issues including changes in strains and the collection of vaccine effectiveness data.

All amendments foreseen will contribute to addressing the need for safe and effective influenza vaccines including those used during zoonotic flu outbreaks taking new scientific knowledge and lessons learned from the Covid-19 pandemic into account.

7. Interested parties

EMA: BWP, PRAC, PDCO, CHMP, NcWP, CTCG

EDQM and OMCLs

External parties: pharmaceutical industry and IMI consortia, academic networks and learned societies within the EU, patients and health care professional representatives.

8. References to literature, guidelines, etc.

Not applicable