EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for medicinal products for human use

Concept paper on the development of an addendum to the Guideline on clinical development of vaccines on clinical trials for vaccines for immunocompromised individuals

Agreed by the Vaccine Working Party	June 2023
Agreed by the Emergency Task Force	July 2023
Adopted by CHMP for release for consultation	12 October 2023
Start of public consultation	1 November 2023
End of consultation (deadline for comments)	30 January 2024

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

Keywords	immunocompromised, clinical trials, immunogenicity, vaccines

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1. Introduction

Immunocompromised individuals comprise a heterogeneous population encompassing a large range of types and degrees of immunosuppression (1). Infections and the complications of infections are a major cause of morbidity and mortality in individuals with primary or secondary immunodeficiencies. Vaccination is among the most effective healthcare measures available for the prevention of infections in immunocompromised individuals but different doses and/or regimens are sometimes required compared to those that are appropriate for the immunocompetent (2).

Immunocompromised individuals are commonly excluded from the clinical trials conducted before the first licensure of new vaccines to avoid confounding of the immunogenicity and efficacy data. Therefore, it is common that there are no or very limited data available from immunocompromised individuals when vaccines are first marketed so it is unknown if the dose regimen recommendations for immunocompetent persons are appropriate for some or all of the immunocompromised population. Furthermore, some live vaccines are never tested in certain types of immunocompromised persons due to the perceived risks.

Post-authorisation studies in immunocompromised individuals, whether required or optional at the time of first marketing authorisation and conducted by the marketing authorisation holder or by other investigators, may face slow recruitment leading to early termination and/or may not provide useful information that can guide the need for and application of alternative dose regimens. As a result, there may be suboptimal dosing regimens and reduced vaccine coverage in the immunocompromised population (4, 5).

2. Problem statement

The Guideline on clinical evaluation of vaccines EMEA/CHMP/VWP/164653/05 Rev. 1 (3) does not provide detailed guidance on the design of clinical trials to assess the safety, immunogenicity and efficacy of vaccines in immunocompromised individuals. There is a need to provide some guidance on potentially suitable sub-populations of immunocompromised individuals for trials to improve the extrapolation of the findings to other sub-populations. Moreover, to consider designing studies in immunocompromised individuals that not only document whether immune responses are lower than in the immunocompetent population but also give some indication of alternative doses and/or regimens that could provide adequate levels of protection against infectious diseases.

3. Discussion (on the problem statement)

There is a need to supplement the Guideline on clinical evaluation of vaccines (EMEA/CHMP/VWP/164653/05 Rev. 1) to address vaccine clinical development programmes in immunocompromised individuals. Examples of issues to be addressed in the supplemental guidance may include the following:

- Design of safety and immunogenicity studies in immunocompromised individuals and how efficacy in the immunocompromised population could be inferred;
- Definitions of and considerations for immunocompromised subpopulations in which to conduct studies, depending on the epidemiology and pathogenicity of the infectious agents in question and the type of vaccine;
- Selection of immunocompromised subpopulations that are sufficiently large to be feasible for clinical trial conduct and which could improve the extrapolation of findings across immunocompromised individuals (e.g. consideration of subpopulations such as solid organ transplant and hematopoietic stem cell recipients, HIV-infected persons, asplenic persons and those with specific types of congenital immunodeficiencies);
- Investigation of the possible need for alternative doses and/or dose regimens in the immunocompromised as part of studies intended to determine the effect of immunocompromised status on immune responses;
- Consideration of specific safety concerns and implications for the safety database in immunocompromised individuals.

4. Recommendation

The Vaccine Working Party and the Emergency Task Force recommend the development of an Addendum to the Guideline on clinical evaluation of vaccines (EMEA/CHMP/VWP/164653/05 Rev. 1) to address the issues identified above. The Addendum would provide guidance on appropriate clinical studies to be conducted in immunocompromised individuals before or after initial marketing authorization to evaluate the need for alternative dose regimens and to support inclusion of specific recommendations for use of vaccines in this population or in specific sub-populations in the Product Information.

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 – 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: Q2/Q3 2024 followed by 6 months public consultation

Expected finalisation: 2025

Resource requirements for preparation

The guidance will be developed by an estimated 2-4 members of the Vaccine Working Party with additional input provided by the ETF.

6. Impact assessment (anticipated)

An impact is expected on the content of future pre-approval and/or post-approval clinical development programmes, on CHMP scientific advice for vaccines and on the responses that the Working Party and the ETF may provide on requests to the CHMP on vaccine-related issues.

7. Interested parties

EMA: PRAC, PDCO, CHMP, CTCG, patients and health care professional representatives

External parties: pharmaceutical industry, academic networks and learned societies, NITAGs and national public health authorities, vaccine advisory boards.

8. References to literature, guidelines, etc.

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5. Lee ARYB, Wong SY, Chai LYA, Lee SC, Lee MX, Muthiah MD, Tay SH, Teo CB, Tan BKJ, Chan YH, Sundar R, Soon YY. Efficacy of covid-19 vaccines in immunocompromised patients: systematic review and meta-analysis. BMJ. 2022 Mar 2;376:e068632.