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Addendum to the Guideline on clinical development of vaccines to address clinical trials in immunocompromised individuals

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1. Introduction

Immunocompromised individuals comprise a heterogeneous population with a large range of types and degrees of immunodeficiency affecting humoral and/or cellular immunity that may result from one or more of:

- Congenital conditions affecting the immune system
- Underlying diseases that result in selective or broad immunodeficiency
- Iatrogenic interventions leading to immunosuppression

Individuals from these groups may be considered to have a clinically important immunodeficiency whenever there are data to indicate that they are at a considerably higher risk of acquiring and/or

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developing severe forms of one or more types of infectious diseases compared to the generally immunocompetent population.

Infections and the complications of infections are a major cause of morbidity and mortality in individuals with clinically important immunodeficiencies. Vaccination is among the most effective healthcare measures available for the prevention of infections in these individuals but different doses and/or regimens are sometimes required compared to those that are appropriate for the immunocompetent. Furthermore, live attenuated vaccines are generally considered unsuitable for individuals with immunodeficiencies.

Immunocompromised individuals are commonly excluded from clinical trials conducted before the first marketing authorisation of a vaccine to avoid confounding interpretation of the immunogenicity and (if generated) efficacy data. Therefore, it is common that there are no or very limited data available from immunocompromised individuals when vaccines are first marketed, which leads to uncertainties regarding appropriate dose regimen recommendations.

Post-authorisation studies in immunocompromised individuals, whether required or optional at the time of the initial marketing authorisation, may not provide information on the need for alternative doses and/or dose regimens, which may result in the use of suboptimal posology.

In summary, there is a clinical need to generate appropriate evidence to identify appropriate dose regimens for immunocompromised individuals.

2. Scope

The Guideline on clinical evaluation of vaccines EMEA/CHMP/VWP/164653/05 Rev. 1 does not provide detailed guidance on the design of clinical trials to assess the safety, immunogenicity and efficacy of vaccines in immunocompromised individuals. This Addendum to the guideline provides guidance on clinical studies to be conducted in immunocompromised individuals before or after initial marketing authorization of vaccines in order to support recommendations for use in the Product Information. The guidance is applicable to all age groups for which the vaccine under evaluation is suitable.

This guidance does not address the investigation of the effects of immunosenescence alone on the immunogenicity or efficacy of a candidate vaccine. It also does not address investigation of the effects of common diseases that are associated with milder forms of immunodeficiencies predisposing to acquisition of certain types of infection (e.g. diabetes, chronic renal disease). It is generally expected that any such effects can be evaluated from interrogation of subgroup data obtained in clinical trials that target the generally immunocompetent population and which minimize exclusions.

Moreover, this guidance does not address clinical development programmes for vaccines intended only for use in immunocompromised individuals or in specific subgroups (i.e. vaccines not intended for a generally immunocompetent population). In such cases, applicants should consult EMEA/CHMP/VWP/164653/05 Rev. 1 and should seek scientific advice from CHMP on the clinical development programme.

3. Legal basis and relevant guidelines

This guidance should be read in conjunction with the Guideline on clinical evaluation of vaccines (EMEA/CHMP/VWP/164653/05 Rev. 1).

4. Design of safety and immunogenicity studies in immunocompromised individuals

4.1. General considerations

During the planning of the clinical development programme for a new vaccine, the need to conduct and the timing of clinical trials in immunocompromised individuals should be considered according to a) the vaccine construct; b) its intended use; and c) the relevance of any available data in immunocompromised individuals with licenced vaccines of the same construct and antigen content as the candidate vaccine.

Whereas non-live vaccines should be potentially suitable for administration to immunocompromised individuals, a decision on the possible conduct of clinical trials with a candidate live vaccine (e.g. live attenuated and live viral vector vaccines) in one or more subsets of immunocompromised individuals should be delayed until there are safety and immunogenicity data, with or without efficacy data, supporting use in immunocompetent individuals.

If the dose regimen in immunocompetent individuals is the same across all age groups for the vaccine under evaluation, it may suffice to conduct a study in a selected immunocompromised population with a specific age range and extrapolate the findings to other age groups. However, if the dose regimen for immunocompetent individuals varies by age, separate studies that evaluate different regimens may be necessary to support age-specific recommendations.

4.2. Objectives of clinical trials in immunocompromised individuals

In the vast majority of cases, the clinical efficacy of a candidate vaccine will not be evaluated in immunocompromised individuals. However, whenever a pre-licensure efficacy trial is to be conducted for a candidate vaccine, applicants should consider which, if any, immunocompromised individuals might be enrolled.

It is expected that clinical trials in immunocompromised individuals will document the safety and immunogenicity of various test dose regimens, including the regimen considered suitable or already approved for immunocompetent individuals in the same age range. Such trials may include a control group of immunocompetent individuals or, with adequate justification and application of the same assay(s) to describe immune responses, a cross-study comparison with an immunocompetent cohort may be acceptable.

In this way, trials can a) describe differences in safety and immunogenicity between groups of immunocompetent and immunocompromised individuals given the same dose regimen (i.e. that suitable for the immunocompetent); and b) compare the safety and immunogenicity data from these two groups with data obtained from groups of immunocompromised individuals randomised to receive

alternative dose regimens. Alternative dose regimens may include one or more differences in amounts of antigen(s) per dose, number of doses and time intervals between doses.

4.3. Trial population:

It is recognised that it is not feasible to study the safety and efficacy of candidate vaccines in every subset of immunocompromised individuals that might potentially derive a benefit. For example, there are numerous types of primary immunodeficiency that can selectively affect humoral or cell-mediated immune mechanisms (e.g. X-linked agammaglobulinemia, chronic granulomatous disease, complement defects), many of which are very rare conditions. Therefore, it would not be appropriate to enrol a mixed population of individuals with primary immunodeficiencies. In addition, in most instances it is unlikely to be feasible to enrol sufficient numbers with any one type of primary immunodeficiency to be able to draw reliable conclusions that then could be extrapolated to other immunocompromised populations.

Having considered the disease(s) to be prevented by a candidate vaccine and what is known about the relative importance of humoral and cell-mediated immunity for protection, it is recommended that applicants identify one or more subgroups of immunocompromised individuals that a) are sufficiently numerous to facilitate recruitment into adequately sized trials; and b) from which results may be broadly extrapolated to relevant subgroups of immunocompromised individuals which may be candidates for the vaccine in clinical practice. For example, a feasible trial may enrol recipients of solid organ transplants or those undergoing certain types of chemotherapy, both of which may exhibit considerable humoral and cell-mediated immunodeficiencies. Another population to consider may include patients with chronic inflammatory conditions on treatment with immunosuppressant/immunomodulatory medications. This group includes an important number of patients, some of which receive lifelong treatment. If a trial in such individuals with both humoral and cellular immunodeficiencies identifies an alternative vaccine dose regimen that elicits immune responses comparable to those achieved with the recommended regimen in immunocompetent individuals, this regimen may be considered applicable to a broad range of immunocompromised individuals. With numbers increasing, applicants could also consider trials that enrol allogeneic hematopoietic cell transplant patients and patients treated with Chimeric Antigen Receptor (CAR) T-cells or bispecific T-cell engaging antibodies.

If the applicant wishes to conduct a single trial in which immunocompromised individuals from more than one distinct subgroup are enrolled, consideration should be given to stratification according to the underlying reasons for immunodeficiency and/or pre-determined capping of numbers. In such cases, it may be appropriate that the primary analysis is based on all immunocompromised individuals, in which case descriptive analyses of data by defined subgroups should be planned.

A further consideration for clinical trial populations is the recognised relationship between very specific subgroups of individuals and the risk of acquiring certain infectious diseases. For example, the risk of invasive infections due to encapsulated bacteria in those with asplenia and the risk of tuberculosis in those treated with inhibitors of TNF alpha. Thus, for certain candidate vaccines it would be especially pertinent to investigate immune responses to standard or alternative vaccine regimens in such individuals.

Finally, it is not anticipated that the safety and immunogenicity of live vaccines (including live attenuated bacterial or viral vaccines and live vectored vaccines) will commonly be evaluated in immunocompromised individuals since use of such vaccines is generally precluded, especially in case of severe primary humoral or cellular deficiencies or profound iatrogenic immunosuppression. Nevertheless, for certain candidate vaccines it may be considered possible and appropriate to proceed with caution into conduct of clinical trials in carefully selected populations.

4.4. Statistical considerations

As indicated in section 4.2, clinical trials in immunocompromised individuals should aim to describe the effect of immunodeficiencies (in accordance with the population) by comparing immune responses (directly or indirectly) between immunocompetent and a selected immunocompromised population when given a dose regimen deemed suitable for the immunocompetent. In addition, it is recommended that within the same trial immunocompromised individuals should be randomised to this standard regimen group or to one or more potential alternative regimen groups.

Due to anticipated limitations of numbers enrolled, especially if multiple alternative dose regimens are to be compared in parallel, it may not be feasible to plan for a formal analysis of non-inferiority of immune responses between the test and control groups. In such cases, it could be acceptable that all analyses are descriptive in nature but the applicant should give consideration to feasible numbers anticipated to be enrolled in a reasonable timeframe and should consider the ability of the trial to rule out potentially unsuitable alternative regimens.

Please consult the Guideline on clinical evaluation of vaccines (EMEA/CHMP/VWP/164653/05 Rev. 1) for further recommendations on selecting primary immune parameters for comparisons between groups, depending on whether or not there is an established immune correlate of protection or threshold value that may be applied.

4.5. Safety

Please consult the Guideline on clinical evaluation of vaccines (EMEA/CHMP/VWP/164653/05 Rev. 1) for general recommendations on the assessment of vaccine safety. Safety data should be summarised separately for each cohort of immunocompetent and immunocompromised subgroups included in the trial. Additional safety considerations for clinical trials in immunocompromised individuals should be assessed on a case by case basis (i.e. monitoring underlying diseases or conditions, such as changes in immunosuppressive therapy requirements or laboratory testing to examine transplant status).