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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

CONCEPT PAPER FOR A GUIDELINE ON THE CONDUCT OF PHARMACOVIGILANCE FOR VACCINES

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Comments should be provided preferably by e-mail to phvwp@emea.eu.int, or otherwise by fax on +44 20 7418 8668, using the appropriate template.

KEYWORDS	Concept Paper, Guideline, Clinical Safety, Pharmacovigilance, Surveillance, Risk Management, Vaccines, Immunisation, Infectious Diseases, Children

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1. INTRODUCTION

This concept paper proposes the development of a guideline on the conduct of pharmacovigilance for vaccines and outlines the special situation of vaccines used by all age groups. It describes these aspects in terms of the steps in the pharmacovigilance process, types of vaccines, different target populations and different stakeholders.

Vaccines are a heterogeneous class of medicinal products containing antigenic substances capable of inducing specific, active and protective host immunity against infective agents or toxins, or against other important antigenic substances produced by infective agents. This concept paper focuses on vaccines used for prophylaxis against infectious diseases. Therapeutic vaccines (e.g. viral-vector based gene therapy, tumour vaccines and anti-idiotypic vaccines such as monoclonal antibodies used as immunogens) will not be considered.

2. PROBLEM STATEMENT

In contrast to other biological and chemical medicinal products used for the treatment of diseases, vaccines are a preventive measure usually given to large cohorts of healthy subjects, especially small children. A guideline will address that (prophylactic) vaccines are different from most other medicines in ways that influence safety considerations. Consequently, a very high standard of safety is generally expected. Furthermore, the exposure to vaccination is virtually universal for many vaccines leading to divers and mainly large target populations.

Consequently it is necessary to consider carefully how pharmacovigilance should be conducted for vaccines and whether there are any aspects of the pharmacovigilance system that need to be enhanced to ensure adequate protection of public health.

Vaccine safety issues have been discussed increasingly in the public area. Several safety signals have raised serious concerns of the public and have reduced the liability and acceptance of vaccines with potential impact on the effectiveness of vaccination programmes. The guideline will focus on methods and tools to investigate the tolerability and safety of vaccines.

Any safety concern arising with a vaccine will concern a very high number of subjects. Therefore, safety concerns need to be quickly evaluated. Although, vaccination programmes might differ between Member States, the same vaccines are authorised and sold across Member States. Therefore, any problem arising with a vaccine in one Member State might have impact on the safety of the same or similar vaccines in all other countries. As immunisation now becomes universal, surveillance should also be universal. New vaccines with an expected large benefit for public health are being developed or currently tested in clinical trials (e.g. anti-malaria, anti-HIV, vaccines for prophylaxis of cervical cancer) and benefit-risk evaluations have to consider safety and efficacy aspects for the individual vaccines and public health. A guideline will point out that validated, robust and widely accepted methods are needed for vaccine safety surveillance.

3. DISCUSSION

3.1 Main Topics

Vaccines are usually given to healthy individuals. Often no immediate individual health benefit can be obtained for the vaccine. Therefore, whereas even common and potentially life-threatening side effects of an anti-cancer therapy are considered to be acceptable, adverse reactions in the case of vaccines are less tolerated, especially if the incidence of the infectious disease in the target population is low or is reduced as a result of a successful vaccination campaign.

The following points should be addressed:

- due to the lower acceptance of risk, intensive investigation of even rare suspected adverse reactions;

- the need for clear case definitions of adverse reactions following use of vaccines for proper case ascertainment and assessment (e.g. Brighton Collaboration);
- the need for long- term follow up for delayed adverse reactions in a post-marketing setting;
- non-serious adverse reactions, which may have impact on the acceptability of a vaccine that translates into a low coverage rate;
- age relatedness of adverse reactions;
- methods to assess causal association of serious and rare adverse reactions;
- special risks for infection of others associated with the administration of live attenuated vaccines;
- batch relatedness of adverse reactions, given that vaccines are biological products with some variation in the manufacturing process between batches; and
- proper post-marketing investigation and assessment of changes in the manufacturing process which, even if small, may have implications on the safety profile of a vaccine.

The role of different stakeholders will be considered:

- Competent Authorities;
- Health authorities responsible for vaccination programmes and for batch release;
- Authorities evaluating epidemiology of vaccine-preventable infectious diseases;
- Healthcare Professionals;
- Vaccinees (paediatric population) and parents (consumer);
- World Health Organization (WHO);
- Marketing Authorisation Holders/Industry/Manufacturers; and
- Media.

The safety aspects in different target groups will be addressed, e.g.:

- Infants with a developing immune system;
- Immuno-compromised patients and
- Elderly patients.

The safety considerations of different types of vaccines will be addressed:

- Live virus and bacterial attenuated vaccines;
- Killed vaccines including vaccines based on bacterial proteins, polysaccharides, protein-conjugated polysaccharides and recombinant protein vaccines;
- New vaccines with new concepts and new technologies such as new delivery systems;
- Vaccines with new adjuvants and alternative routes of administrations; and
- Combined vaccines

The special safety aspects of stabilisers, preservatives, adjuvants and other residual material from the manufacturing process in the final product.

3.2 Preparation of Pharmacovigilance in the Pre-Authorisation Phase

Cross-reference to the revised guideline on the clinical testing of vaccines should be made (CHMP Guideline on the Clinical Evaluation of Vaccines (CHMP/VWP/164653/2005). It has to be considered that pharmacovigilance planning is an essential element of the application for marketing authorisation (see CPMP/ICH/5716/03). If necessary, a Risk Management Plan should be submitted in accordance with the Guideline on Risk Management Systems for Medicinal Products for Human Use (EMEA/CHMP/96268/2005).

3.3 Post-Authorisation Pharmacovigilance

The guideline will address the post-authorisation pharmacovigilance concept, taking into account that new vaccines and old (well established vaccines) have different aspects and requirements.

3.3.1 Signal Identification

- Spontaneous Reports
  - Case definition, case ascertainment and case documentation

    The appropriate case ascertainment is crucial for a valid spontaneous reporting system. Marketing Authorisation Holders and Competent Authorities should develop predefined check lists or formats for those adverse reactions which can be anticipated from the experience with comparable vaccines to be reported after authorisation (e.g. SIDS in temporal association with vaccines in infants). This is essential to ascertain relevant clinical information in a consistent way in order to ensure the high quality of the causality assessment of an individual case. The definitions of the Brighton Collaboration should be considered if appropriate[1]. Adequate follow-up of serious spontaneous adverse reaction reports should be guaranteed.
  - Causality assessment

    The importance of causality assessment (e.g. WHO criteria) will be stressed. The following categories of adverse events following immunisation should be considered:

    1. Vaccine induced adverse reactions following immunisation: those due to the intrinsic characteristics of the vaccine preparation and the individual response;
    2. Vaccine precipitated. Those triggered by administration of a vaccine but may also have occurred later or in other circumstances;
    3. Other events: including GMP errors, contamination, administrative errors, vaccine storage errors;
    4. Coincidental, only temporally related, not due to immunisation.
  - Handling of Consumer reports

    A guideline would describe how Consumer report provides additional value to the information from Healthcare Professionals, how they can be validated and used for signal detection. Recommendations regarding education, promotion and facilitation of adverse reaction reporting will be included.
  - Vaccine failures as expedited reports

    A guideline will give advice how to handle cases of vaccine failure, including consideration of:

    - Clear case definition;
    - Validated analytical methods;
    - Documentation of proper handling of immunisation; and
    - Evaluation of risk factors (e.g. obesity, age, smoking status).

    If there is concern of a higher than expected rate of vaccine failures in certain risk groups an appropriate systematic post-marketing surveillance study should be initiated.
- Periodic Safety Update Reports (PSURs)

  Specific aspects for vaccines should be addressed in the PSUR:

[1] See http://www.brightoncollaboration.org/internet/en/index.html.

- Impact of changes of the manufacturing process on safety;
- Batch relatedness of adverse reactions and other (quality) problems;
- Vaccines failures/lack of effect. Reports on vaccine failure/ lack of efficacy should be summarised and assessed in a separate chapter;
- Relevant literature information concerning stabilisers, preservatives and adjuvants and products with comparable antigens;
- Concomitant administration: If concomitant vaccination (either simultaneous or mixed administration) with another vaccine is specifically mentioned in the SPC, safety aspects of the concomitant administration should be analysed; and
- Safety aspects of different vaccination schedules and different dosages (adults, children).

3.3.2 Signal Quantification and Evaluation

- Post-Marketing Studies

  Post-marketing safety studies should investigate adverse reactions/risks, which are not identified and/or fully characterised prior to authorisation such as:

  - Rare but serious adverse reactions;
  - Reactions with delayed onset; and/or
  - Reactions in subpopulations.

  Ideally, post-authorisation surveillance of vaccine safety provides reliable estimates of the incidence of adverse reactions in the target population, the causal relationship between vaccine and adverse event and risk factors predisposing to specific adverse events. A guideline would present specific advice and considerations when and how specific studies should be conducted.

- Data Management

  Data retrieval and analysis should consider relevant factors for vaccines such as:

  - Age (e.g. premature infants, neonates, infants, the elderly);
  - Number of doses;
  - Batch numbers;
  - Different vaccination schedules; and
  - Defined risk factors or underlying diseases.

3.3.3 Risk Minimisation and Regulatory Action

In addition to conventional tools for risk minimisation a guideline would also consider that risk minimisation may be based on a precautionary measure, which takes into account that vaccination is a preventive intervention usually given to healthy individuals. A guideline would describe the principles of adapting the precautionary principle to the conditions of vaccines.

3.3.4 Benefit-Risk Assessment

A guideline will highlight that the potential for any risk is considered less acceptable in the case of vaccines than in the context of disease treatment. The risk-benefit balance of a vaccine has to address both population and individual health aspects.

A guideline would address that the risk-benefit balance for vaccines depends highly on the incidence of the infectious disease in the target population, the proportion of infected persons with clinical disease, as well as the risk of transmission, identification of high-risk groups and geographical and seasonal characteristics of the infectious disease. A guideline would explain why the benefit-risk assessment of a vaccine changes over time and may differ between different target populations. For vaccines included into the extended vaccination programme the impact of the vaccine on the

epidemiology of the vaccine preventable condition should be considered. If the incidence of the infectious disease has been decreased or eradicated due to the effectiveness of a vaccine, even rare adverse reactions have to be taken into account and the new risk-benefit balance may change significantly. As a consequence, the public demands greater vaccine safety as immunisation has progressively controlled or eliminated vaccine-preventable diseases.

The need for relevant expertise, including independent expert advice when considering a benefit-risk assessment of vaccines will be stressed in a guideline.

3.4 Vaccine Risk Communication

The guideline would describe the special environment and conditions of risk communication in the area of vaccination. Key principles and lessons learned from public perception of risks and waning trust of the public in immunisation will be discussed. A guideline would describe that the level of trust in immunisation is usually high at the beginning of an immunisation programme when the disease is frequent and patients and healthcare providers have personal experience with the disease (e.g. polio, diphtheria). As immunisation programmes successfully reduced the incidence of vaccine-preventable disease the proportion of vaccinees and healthcare providers, who do not have personal experience with the disease, are increasing. They have to rely on historical and other more distant descriptions for their subjective analysis. This situation significantly influences the risk perception. A guideline would also discuss that risk perception may differ between stakeholders (health authorities, industry and public) especially if there is uncertainty of scientific evidence about the scientific evidence of the risk.

4. RECOMMENDATION

The purpose of this concept paper is to highlight the need of a pharmacovigilance guideline for vaccines in the EU. Therefore it is proposed that the CHMP Pharmacovigilance Working Party in collaboration with the CHMP Vaccine Working Party, the CHMP Biotechnology Working Party and the CHMP Paediatric Working Party should develop this guideline, taking account of the points discussed above.

The guideline is aimed to give guidance to Marketing Authorisation Holders, Competent Authorities and with regard to certain aspects also committees responsible for vaccination programmes.

The proposed guideline will not replace the relevant pharmacovigilance guidelines. The document should be seen in the context with the relevant regulation and guidelines for the conduct of pharmacovigilance (see 9.).

The guideline will highlight specific aspects performing pharmacovigilance for vaccines. Close collaboration between pharmacovigilance experts and experts/institutions in charge for vaccination programmes and national laboratories responsible for vaccine batch testing and release is important.

5. PROPOSED TIMETABLE

The following timetable is proposed:

Release of draft Guideline for public consultation: March 2007

Deadline for comments: September 2007

Re-discussion in PhVWP/VWP/PEG: October 2007 to January 2008

Expected date for adoption of final Guideline by CHMP: February 2008

6. RESOURCE REQUIREMENTS FOR PREPARATION

It is estimated that the following resources are required:

2 Rapporteurs at the level of the PhVWP, 4 PhVWP Plenary discussions, 2-4 Drafting Group meetings, involvement of VWP and PEG.

7. IMPACT ASSESSMENT (ANTICIPATED)

It is expected that the Guideline will strengthen the safety assessment for vaccines. Consequently, the safety of vaccines and their use should be improved. This should also positively impact on the acceptance of vaccination programmes. Safe and effective use of vaccines is of major public health relevance.

8. INTERESTED PARTIES

Pharmaceutical industry, in particular vaccine manufacturers, Competent Authorities and vaccination programme committees (public health authorities) in Member States, World Health Organization (WHO)

9. REFERENCES TO LITERATURE AND GUIDELINES

- Volume 9A of the Rules Governing Medicinal Products in the EU;
- Note for Guidance III/3375/93: Clinical Safety Data Management – Definitions and Standards for Expedited Reporting (ICH-E2A);
- CPMP/ICH/3945/03: Post-Approval Safety Data Management – Definitions and Standards (ICH-E2D);
- CPMP/ICH/288/95: Clinical Safety Data Management – Periodic Safety Update Report for Marketed Drugs (ICH-E2C);
- CPMP/175/95: Clinical Safety Data Management – Data Elements for Transmission of Individual Case Reports Electronic Transmission (ICH-E2B);
- Detailed Guidance on the Collection, Verification and Presentation of Adverse Reaction Reports Arising from Clinical Trials on Medicinal Products for Human Use (ENTR/64422);
- CPMP/ICH/5716/03: Planning of Pharmacovigilance Activities (ICH-E2E); and
- EMEA/CHMP/96268/2005: draft Guideline on Risk Management Systems for Medicinal Products for Human Use.