The European Agency for the Evaluation of Medicinal Products
Evaluation of Medicines for Human Use

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CONCEPT PAPER ON CONDUCT OF PHARMACOVIGILANCE FOR MEDICINES USED BY CHILDREN

1. Objectives of the Concept Paper

This paper outlines the special situation with regard to pharmacovigilance of medicines used by children and describes this in terms of the steps in the pharmacovigilance process, types of medicinal product and different stakeholders. This paper proposes the development of a guideline on the conduct of pharmacovigilance for medicines used by children.

2. Problem Statement

The efficacy and safety of medicines may be different in children compared to adults. The available documentation at the time of approval is, in general more sparse in children and long term data collection may be needed in order to clarify the safety profile in children and particularly to detect any long-term or delayed toxicities in the developing child. Therefore, there is a need to carefully consider how pharmacovigilance is conducted for medicines used by children and whether there are any aspects of the pharmacovigilance system that need to be enhanced to ensure adequate protection of public health. Furthermore, many medicines used to treat children are not licensed for such use (off-label use) or are not licensed at all (unlicensed use). This may further limit reporting of suspected adverse reactions to the pharmacovigilance systems.

3. Background and Need for Guidance

3.1 Medicines for Children

This concept paper should be seen in the context of the various strategies in place or in development to deal with the issue of provision of licensed medicines for children. In many countries around the world including EU Member States, there has been a realisation that the lack of medicines specifically licensed for children is unsatisfactory. At a European level the Committee for Proprietary Medicinal Products (CPMP) has set up a Paediatric Expert Group (PEG) and the European Commission has made proposals for a Paediatric Regulation. As well as focusing on the licensing of medicines for children, these European strategies also need to ensure that post authorisation safety monitoring (pharmacovigilance) is robust.

The first products with orphan medicinal product status are now being authorised in the EU. Many of these products will be for rare childhood diseases and the data on safety and efficacy at the time of licensing is likely to be limited in several cases.

3.2 Pharmacovigilance for Children's Medicines

Various issues about medicines used by children increase the need for effective pharmacovigilance. Some of the key issues are set out below:

- Childhood diseases may be qualitatively and quantitatively different from adult diseases.
- Efficacy in children cannot always be assumed from adult efficacy data.
- Children may have different pharmacokinetics and dynamics to adults and therefore have particular vulnerability to Adverse Drug Reactions (ADRs).

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- Children may have different drug metabolism and consequently a different drug interaction profile compared to adults. Due to specific ethical considerations drug metabolism data in children may be very sparse at the time of registration.
- Children are growing and may therefore be susceptible to developmental disorders, as well as, delayed ADRs not seen in adults.
- Certain ADRs may only be seen in children.
- Lack of clinical trials in children limits the safety data available.
- Lack of kinetics data may lead to under or over-dosing in some age groups.
- Under-dosing may result in lack of benefit or development of resistance.
- Over-dosing may result in an increase of Type A reactions.
- Lack of appropriate formulations may lead to incorrect dosing and use of products of less controlled quality.
- Children may be more susceptible to ADRs from specific excipients.
- Medicines used off-label may have inadequate product information to support safe use in children.

Premature babies may be at a much higher risk (for example due to undeveloped drug eliminating organs, distribution barriers and physiological regulatory functions) and therefore need further enhanced pharmacovigilance.

3.2.1 Pharmacovigilance Assessment at the Time of Licensing

A Paediatric Pharmacovigilance Guideline should address the issue of pharmacovigilance assessment at the time of licensing. Such an assessment would be based on the fact that when medicines are licensed for children, the clinical trials database for both efficacy and safety may be very limited. The pharmacovigilance assessment would highlight areas where data were lacking (i.e. safety had not been demonstrated), highlight potential risks for using the medicines in children and suggest both post-authorisation safety data collection mechanisms (e.g. post-authorisation safety studies) and risk reduction strategies. The guideline would discuss the use of pharmacogenomic methodology to monitor adverse reactions prospectively.

3.2.2 Pharmacovigilance for Products on the Market

The subsequent sub-sections highlight how specific problems may occur with aspects of the pharmacovigilance process, when dealing with medicines for children and where a guideline should deal with these. Particular emphasis is placed on data collection as this is considered the critical specific need.

3.2.2.1 Data Collection

Effective pharmacovigilance requires effective capture of data relevant to the safety of medicines. Such data are used for both signal detection and signal evaluation. Spontaneously reported suspected ADRs remain the most important source of detecting safety issues in the post authorisation phase. However, in addition to the well-known limitations of spontaneous reporting systems, children may be poor at expressing symptoms that may therefore not be detected. Furthermore, parents represent an additional step between clinical event and a report of suspected ADR reaching the regulator. A Paediatric Pharmacovigilance Guideline would explore the roles of different groups of reporters (including patients/parents) and make recommendations regarding education, promotion and facilitation of ADR reporting.

Periodic Safety Update Reports (PSUR) are key public health documents produced by the industry as laid down in ICH E2C[1] and European legislation. A guideline will give specific

[1] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), ed. Clinical safety data management: periodic safety update reports. Geneva: ICH; 1996.

consideration to whether use in children should be documented in the PSUR, when a PSUR should specifically consider the safety of a product in children, when off-label use should be considered and when extending the indication of a medicine to children should trigger re-starting the PSUR clock.

Published literature is another important source of pharmacovigilance data. A guideline would address the need to specifically search paediatric literature.

Post authorisation safety studies fall into three broad categories:

1) Those designed to demonstrate safety (large numbers of patients studied to expand the safety database).

2) Those aiming to detect new safety issues (detecting hazards).

3) Those to evaluate known safety issues (e.g. those detected in the pre authorisation phase).

A guideline would give specific advice on when such studies should be conducted and any specific considerations on how they should be conducted on medicines used in children. Particular consideration will be given to what methodologies might be employed to detect long-term, delayed and developmental ADRs.

3.2.2.2 Data Management

A guideline would stress the importance of managing data in a form that allows data retrieval and analysis by age. Recommendations would be made for stratifying data by age.

3.2.2.3 Signal Detection

A drug safety signal can be a previously unrecognised safety issue, a change in the frequency or severity of a known safety issue or identification of a new at risk group. A Pharmacovigilance Guideline would explore how these different aspects should be addressed in signal detection for children. The guideline would suggest using statistical methodologies to increase the chances of detecting signals for children from various data sources. The guideline would also discuss the difficulties in detecting delayed or chronic toxicities including effects on development.

3.2.2.4 Risk Evaluation

A guideline would outline the need to estimate exposure and therefore risk in different populations.

3.2.2.5 Benefit Risk Assessment

The CIOMS IV Working Group Guideline[2] on benefit risk assessment already stresses that all populations and indications should be assessed for benefit and risk during a benefit risk assessment. A Paediatric Pharmacovigilance Guideline would reinforce this and stress the need for relevant expertise, including independent expert advice when considering a benefit risk assessment of medicines used by children.

3.2.2.6 Regulatory Action

The various regulatory and risk reduction tools that are available for medicines used by adults may not all be available when medicines are used by children. For example, if unlicensed medicines are used or medicines are used off-label then this may limit the options available. A Paediatric Pharmacovigilance Guideline would explore the regulatory options available with medicines used for children.

[2] Council for International Organizations of Medical Sciences (CIOMS), ed. Benefit-risk balance for marketed drugs: evaluating safety signals. Geneva: CIOMS; 1998.

3.2.2.7 Communications

A Paediatric Pharmacovigilance Guideline would briefly discuss the use of product information to describe paediatric safety issues with reference to the European SPC Guideline. A guideline would also consider both routine and urgent communications and the need to consider the requirements of both parents and children. A Guideline would discuss how to provide information to users of medicines when safety issues arise from off-label or un-licensed use.

3.2.2.8 Audit and Outcome Assessment

A Paediatric Pharmacovigilance Guideline will reinforce the need to ensure effective audit of the pharmacovigilance process and measurement of the outcomes of any actions taken.

3.2.3 Consideration of Different Product Types

Whether a medicine should be used to treat a particular child with a particular disease (or to prevent a particular disease) requires an evaluation of the benefit risk balance for that intervention in that child. The level of safety expected of a medicine will depend on the disease being treated or the frequency and seriousness of the disease being prevented (see section 3.2.3.3).

3.2.3.1 Licensed Medicines

The guideline would give a brief discussion of how paediatric pharmacovigilance maybe different for licensed medicines when used on and off-label.

3.2.3.2 Unlicensed Medicines

A guideline would make some recommendations regarding specific problems with unlicensed medicines including extemporaneous preparations. A guideline would stress that both companies and regulators should perform pharmacovigilance for unlicensed and off-label use of medicines.

3.2.3.3 Variable exposure to medicines

Orphan diseases are by definition rare and medicines developed for their treatment are likely to have been tested in very few individuals. Furthermore, the mechanisms for detecting new safety signals with extensively used drugs (like spontaneous reporting systems) may be much less effective with drugs with low usage. The Paediatric Pharmacovigilance Guideline will make practical recommendations on how to conduct pharmacovigilance for low usage (including orphan) products.

3.2.3.4 Vaccines

A guideline will address the special aspects of the safety assessment of vaccines. In contrast to other biological and chemical drugs that are used for the treatment of diseases in ill children, vaccines are a preventive measure usually given to large cohorts of healthy children. A guideline will address the special sensitivity of the benefit risk relation of vaccines in healthy children especially when the incidence of the infectious disease in the target population is low or is reduced as a result of a successful vaccination campaign. Whereas, even common and potentially life-threatening side effects of an anti-cancer therapy are considered to be acceptable, the guideline will point out that due to the lower tolerance of risk, it is necessary to intensively investigate even rare suspected adverse drug reactions following vaccination. A guideline will also address the need to follow up for delayed ADRs. Non-serious ADRs may have impact on the acceptability of a vaccine that translates into a low coverage rate. This issue will also be addressed in the guideline. A guideline will highlight that the potential for any risk is considered less acceptable in the case of vaccines than in the context of treatment for an underlying disease.

Several gaps in pre-licensure clinical trials of vaccines are recognised. Sample sizes in Phase I and II trials are usually low and even in phase III trials sample size calculations are mostly based on efficacy assumptions. That means that the sample size usually is limited to the observations of common local and systemic reactions. Serious adverse events after vaccination are rare, and

are generally not observed in the clinical trial programme. Nonetheless, a large number of subjects exposed to a vaccine is desirable in order to assess whether a reaction will occur with a low probability (if at all) in the target population. For certain vaccines it is impossible to properly investigate rare adverse reactions prior to licensure. The guideline will discuss adequate tools to investigate rare adverse reactions via establishment of an active post-marketing surveillance programme, including:

- Post-marketing surveillance studies.
- Ad hoc epidemiological studies.
- Use of large databases linking immunisations and medical outcome.
- Registries.
- Laboratory investigations.

In many EU countries, vaccination programs are organised in a centralised system. This may provide the opportunity to establish registries. The possibility of meta-analysis of different studies for identification of rare adverse drug reactions will be discussed, including the opportunity for standardisation of safety evaluations in clinical trials as a prerequisite to assess rare adverse events across clinical trials.

Completely new vaccines with new concepts, new technologies, new adjuvants and alternative routes of administrations have been developed or are currently in the clinical testing phase. Some have already been licensed in several countries. Novel safety issues may arise. A guideline will give recommendations on targeted monitoring and special surveillance studies required for certain types of rare but serious adverse reactions that can be anticipated from the particular composition of the new vaccine or their relationship to well-established vaccines.

3.2.4 The Role of Different Stakeholders

A Paediatric Pharmacovigilance Guideline would briefly describe the different stakeholders involved and their respective roles and responsibilities. Stakeholders would include:

- Children and their parents.
- Regulatory authorities.
- Industry.
- Healthcare professionals.
- Media.

4. Proposal

The purpose of this concept paper is to highlight the need for a Paediatric Pharmacovigilance Guideline within the EU. It is therefore proposed that such a guideline is produced by the CPMP Pharmacovigilance Working Party in collaboration with the CPMP Paediatric Expert Group. Such a guideline would underpin the other strategies currently being considered by EU regulators and the European Commission.