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Committee for Medicinal Products for Human Use (CHMP)

Position paper on potential medication errors in the context of benefit risk balance and risk minimisation measures

Draft

Focus on medication errors caused by confusion of a newly introduced medicinal product with an existing one, similar in active substance but different in some aspects.

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Comments should be provided using this template. The completed comments form should be sent to *thomas.goedecke@ema.europa.eu*.

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1. Introduction

During the life-cycle of a medicinal product a number of changes may be introduced that have an impact on the use of the product in clinical practice. These changes can be the result of variations, extensions to the MA or extensions of indications of the existing product resulting in a different formulation, presentation, route of administration, strength or composition, as well as a different indication or target patient population. Changes in clinical practice may also arise from the introduction of products referring to a reference medicinal product but differing from the reference product already on the market (with regards to strengths, indication, etc.).

Regardless of the type of regulatory procedure, the introduction of a medicinal product that contains the same active substance but otherwise differs from products previously authorised and subsequently established in clinical use, bears a potential risk of medication errors. The assessment of such changes should include a comparison with existing products on the market in view of the potential risk of medication errors.

In general, medication errors can occur for a variety of reasons. Whether attributable primarily to either the user, be it professional or patient, or to product-related aspects such as presentation or instructions for use, in many cases a combination of unfavourable circumstances will be the cause for erroneous drug administration.

The topic of medication errors has been addressed in the draft Guideline on Good Pharmacovigilance Practices (GVP): Module V – Risk management systems (EMA/838713/2011), in general terms. The purpose of this position paper is to specifically address the risk of medication error that arises where a newly introduced medicinal product could potentially be mistaken for an already established one containing the same active substance and similar in some other attributes such as appearance and/or name but different in strength, dosing, route of administration, etc..

The aim of this position paper is to provide guidance on how the benefits and risks of such products should be weighed and how the risk of medication errors can be adequately addressed.

2. Scope

This position paper focuses on the impact of potential medication errors on the benefit/risk balance of medicinal products introducing changes vis-à-vis an already authorised product containing the same active substance. In these situations an important potential risk of medication error may exist that needs to be evaluated and balanced against any potential advantages the product under evaluation might have over the product which is already established in clinical practice.

From a public health perspective, the following scientific arguments are relevant and emphasise the need for a thorough consideration and a harmonised approach. Factors which may critically increase the risk of medication error as well as criteria specifically underlining the benefit of the products in question need to be carefully reflected and weighed against each other.

The various aspects of benefit and risk as well as measures intended for risk minimisation and monitoring will be addressed in the subsequent chapters.

3. Benefit/Risk discussion

3.1 Potential benefits

Introduction of a product that differs from an established product as regards its concentration or strength, that is presented in a different pharmaceutical form, a new administration device or has a different composition or is intended to be used in a different patient population or indication, etc. may in general be seen as a valuable addition to the therapeutic armamentarium since it may satisfy a justified medical need. On the other hand, such products may carry an inherent potential risk for incorrect use leading to medication errors. Medication errors may in some cases result in serious and/or life-threatening events caused for example by over- or under-dosing, incorrect application via the wrong route of administration or administration to the wrong patient population.

It has to be kept in mind that drug therapy is generally prescribed and administered by well-trained experienced personnel, based on expert decision for treatment and – if drug not intended for self-administration - usually administered according to standardised working procedures. This will help reduce the risk of medication errors, but cannot always prevent them

The benefit-risk ratio has to be carefully considered for each individual product in question. In many cases the benefits of such differing products will outweigh the associated above-mentioned risks of medication errors. Examples of possible benefits may be:

- If excipients such as preservatives and/or antioxidants can be avoided or reduced, patients might benefit from reduced undesirable effects possibly caused by these excipients.
- A different strength or composition may help to improve stability and/or in-use stability of the drug product. Hence patients might benefit from reduced undesirable effects caused by degradation products (due to a more stable medicinal product).
- Another reasoning to justify a different concentration or formulation may be to avoid necessary dilution or at least facilitate preparation (e.g. dilution of a concentrate is easier to handle compared to the multiple steps required to dissolute a powder, prepare a concentrate and further dilute to prepare a ready-to-use solution) to allow for a more accurate dosing. This may not only lead to enhanced safety of the pharmacist/healthcare professional by reducing manipulation steps but also confer indirect benefit for patients because of a reduction of the potential preparation errors. A more appropriate concentration/strength could also provide required flexibility that the original concentration did not allow.
- Different formulations that offer advantages to patients, for example liposomal or other formulations that improve the benefit/risk of the product compared to the original formulation, extended release formulations that improve compliance, or formulations that are easier to administer for patients with dysphagia.
- New types or sizes of primary packages or medical administration devices that facilitate preparation and/or administration. More patient-friendly packaging, adherence-facilitating formulation (e.g. ease of opening, ease of tracking, capsules with pH-meter inserted) or a formulation improving palatability/acceptability.
- Use in specific populations, e.g. children or older people, and/or in additional indications which were not covered by the already existing products.
- Further benefits regarding economic (multi-use instead of single-use preparations might be more economic in use) and/or environmental (multi-use instead of single-use preparations might help to

reduce toxic wastage) advantages might also occur. However, these aspects lie outside the scope of benefit/risk assessment for market approval and will not be further discussed.

3.2 Evaluation of Risks

In all situations similar but not limited to the examples described above, the potential advantages need to be balanced against the additional inherent risk and effects of medication errors, which in turn are dependent on the extent of deviation from the established product, the therapeutic window of the active substance, the severity of adverse effects caused by the individual components of the medicinal product and the measures taken to avoid medication errors. Justification should be provided in the Pharmaceutical Development (3.2.P.2) of the application file as well as in other sections where appropriate (e.g. clinical data, benefit/risk discussion, RMP, etc.). It is important to note that these considerations are complementary to the already known safety profile of an established product.

The following aspects should be considered when evaluating the benefit-risk ratio from a clinical point of view:

- A detailed discussion should be provided on the potential occurrence or increased incidence and/or severity of adverse events as well as a loss of efficacy due to incorrect dosing caused by a medication error. All studies using dosage regimes different to those recommended in the SPC should be taken into account.
- All relevant information should be used to assess whether the medicinal product in question should be regarded as a narrow therapeutic index drug. The judgement should be made following a case-by-case assessment based on clinical considerations. Serious consequences of medication errors are more likely in case of a narrow therapeutic index drug (e.g. cytotoxic drugs) and/or if given to a particularly vulnerable patient population (e.g. immunocompromised patients, paediatric population, pregnant women, elderly, etc.).
- Risks have to be seen in the context of the extent of possible over- or underexposure due to incorrect dosing, incorrect administration route, etc. For example, if the product features double the strength compared to the already approved product, a two times higher dosage might be administered erroneously. The risks of such an incorrect dosage need to be evaluated. Similarly, the risk of potential under-dosing has to be evaluated in case of a lower strength. If a new dosage results in a lack of efficacy this may also have serious consequences.
- The applicant's proposals in the Risk Management Plan to clearly differentiate between the product under evaluation and the established one – e.g. vial size, packaging warnings on vials, etc.

In general, the risk of a medication error due to a product differing from the product established in clinical use cannot be accurately quantified a priori. Nevertheless, certain circumstances that may potentially increase the probability of medication error warrant consideration, such as:

- Is the medicinal product administered by a health care professional or self-administered by the patient?
- Has the healthcare professional/patient undergone some kind of special training in correctly administering the medicinal product?
- Is the product intended for emergency use and does it have to be prepared under time pressure or otherwise stressful situations?

- Is this product intended for children or is it presented in a new way that seems more suitable for children?

The introduction into the market of a product differing from an already established one used routinely in clinical practice may result in an increased risk of medication error. Therefore, the applicant has to justify that the benefits outweigh the potential risks linked with this new product. In addition, when the benefit is well known, specific rules should be applied to reduce the risk.

4. Risk minimisation and monitoring

Routine risk minimisation activities generally identified for any new product to reduce the risk to patients include the provision of product information (SPC, Package Leaflet and labelling), i.e. contraindications, warnings, etc. Additional risk minimisation activities are those which go beyond this and may include controlled distribution, specific physician, pharmacist or patient educational material, patient alert cards, alerts on/in the packaging, etc.

If a specific potential risk is identified for a new product with significant advantages (e.g. such as outlined in section 3) relative to the established product, the following risk minimisation strategies should be discussed on a case-by-case basis:

- Whenever new concentrations/strengths, formulations, new appearance of a dosage form, preparations, addition of excipients, new target populations, etc. are introduced, this has to be highlighted very clearly in SPC, PIL and labelling and if necessary also in a name of a medicinal product as the one most important routine risk minimisation measure. Other measures such as different vial sizes, design of packaging, etc. should also be considered. Proposals for pack design and for new (invented) names should be submitted by the Applicant and agreed prior to approval.
- A user testing, which is able to prove that the instructions how to handle the product are clear and understandable, should be performed and submitted before approval.
- Training pharmacists/healthcare professionals, based on approved educational material, should be offered by the MAH, if there is no possibility to implement all information needed for safe use of the product within SPC, PIL and labelling. A proposal for educational material should be submitted by the Applicant and its key elements should be agreed prior to approval as part of the EU-RMP which is to be submitted and approved prior to the Opinion. The content and format of the educational material will need to be agreed with the National Competent Authority prior to launch within each member state.

If additional risk minimisation measures are required, they should be agreed as conditions for marketing authorisation with the key elements specified as appropriate.

Monitoring of the effectiveness of risk minimisation measures can, for example, be achieved by (see also GVP Module XVI of the new PhV legislation):

- monitoring of medication errors resulting in adverse reactions, e.g. with methods of signal detection.
- and/or commitment to submit PSURs in accordance with the regular periodicity for PSUR submission, starting with every 6 months after authorisation, which should be continued until at least two full years of marketing experience in the EU have been gained.

- shortening of PSUR cycles might also be an approach in regard to monitoring a specific risk.

The effectiveness of all the risk minimisation measures (change of name, product information, educational material, user testing) in place should be re-evaluated in accordance with defined time-intervals, e.g. in PSURs, milestones or updates of the RMP, etc.

5. Recommendations

For new presentations of existing medicinal products, including new indications, patient populations etc., the potential for an increase in risk of medication errors as compared with the original product, should be considered in the development and presentation of the product. With regard to the potentially serious and/or fatal consequences of medication errors the CHMP particularly accentuates the need for a critical assessment of medicines with a narrow therapeutic index and/or destined for a special population (such as paediatric, neonates as well as elderly) in which medication errors are known to occur more frequently and/or in which the consequences of a medication error are generally expected to be more serious.

Following this principle, it will be important that the applicant is able to justify such an application by demonstrating a prevailing benefit to counterbalance the potential product-associated increased risk of medication error. All risk reducing measures (e.g. very clear and prominent labelling in the product information, packaging/vial size difference, etc.) have to be implemented.

Whether the potential advantages compensate for the additional risk of medication errors and a positive benefit-risk balance can eventually be confirmed needs to be based on a comprehensive case-by-case benefit-risk evaluation.

The applicant is advised to engage in collaboration with the regulatory authorities at an early time point when considering the development and submission of an application involving a product that introduces changes to the already established clinical practice.