Aseptic preparation of parenteral medicinal products in healthcare establishments in Europe

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ABSTRACT

In many cases, parenteral medicines with a marketing authorisation cannot be administered directly to patients, that is, they are not presented in ready-to-administer form. Before administration to patients, these medicines have to be reconstituted. Reconstitution has a special position; it can neither be seen as industrial manufacture nor as 'regular' pharmacy preparation. There are other processes in healthcare establishments (eg, parenteral nutrition), related to the reconstitution process, where the requirements of national quality assurance standards for the safe preparation of sterile products are equally important and have to be fulfilled. In European healthcare establishments, aseptic preparation of parenteral medicinal products is considered to be a process of crucial importance for patient safety because errors in the preparation of these medicines may lead to a product that can cause immediate damage to patients. Aseptic preparation of medicinal products is carried out in hospital pharmacies as well as in clinical areas in healthcare establishments. The Committee of Experts on Quality and Safety Standards for Pharmaceutical Practices and Pharmaceutical Care (Council of Europe; hereafter: Committee of Experts), supported by the European Directorate for the Quality of Medicines & Healthcare, is undertaking work on the topic of aseptic preparation of medicines. The work is carried out in cooperation with the European Association of Hospital Pharmacists on the basis of a Resolution CM/Res AP(2011)1 on Quality and Safety Assurance requirements for Medicinal Products prepared in Pharmacies for the Special Needs of Patients, which was adopted by the Committee of Ministers on 19 January 2011. The Resolution includes some recommendations and an outlook to further work on reconstitution of parenteral medicines. A survey that was sent to the different European countries demonstrated that there is no or just limited regulation concerning reconstitution in Europe. This article describes the risks associated with poor reconstitution practices and the previous work as well as the ongoing activities concerning reconstitution at the European level. The article emphasises the need for regulation in this area, which is missing at present. It is expected that consensus can be reached on a guidance document for reconstitution at the European level.

INTRODUCTION

In many cases, parenteral medicines with a marketing authorisation cannot be administered directly to patients, that is, they are not presented in ready-to-administer form. Before administration to patients, these medicines have to be reconstituted. Hospital pharmacies can provide ready-to-administer parenteral products. The reconstitution process,

which precedes administration, may vary from simple preparation to many or very complex operations.

Reconstitution relates to medicinal products with a marketing authorisation not yet ready for use by patients and may take place at different locations in healthcare establishments. There are other processes in healthcare establishments (eg, parenteral nutrition (PN)), related to the reconstitution process, where the requirements of national quality assurance standards for the safe preparation of sterile products are equally important and have to be fulfilled. Aseptic preparation of parenteral medicinal products in healthcare establishments introduces risks for patients' safety. Adequate reconstitution of medicinal products is considered to be of crucial importance for patient safety by national authorities, healthcare establishments and hospital pharmacists.

Reconstitution is defined as the manipulation to enable the use or application of a medicinal product with a marketing authorisation in accordance with the instructions given in the summary of product characteristics (SmPC) or the patient information leaflet. This definition of reconstitution is based on consensus reached among 36 member states of the Council of Europe.¹

From a regulatory point of view, reconstitution has a special position:

1. Reconstitution cannot be seen as a part of industrial manufacture because it is performed outside the industry. Regulation for medicinal products manufactured on an industrial scale is clear and has an international focus; the manufacture has to comply with EU GMP² and a marketing authorisation issued by the competent regulatory authority is required for products before being placed on the market.
2. Reconstitution cannot be seen as a 'regular' pharmacy preparation because the starting material for reconstitution is a medicinal product with a marketing authorisation instead of an active pharmaceutical ingredient and also because reconstitution often occurs in clinical areas instead of pharmacies. The preparation of medicinal products in pharmacies falls under the national competencies, as far as it is not covered in international regulation.
3. Given its special position, a separate paragraph (paragraph 9) was dedicated to reconstitution in the Resolution on pharmacy preparations.¹

In this article, we will focus on the reconstitution of parenteral medicinal products. A working group was instigated to develop a guideline for safe reconstitution. In this article, we will first describe the

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risks of reconstitution, and then focus on how to improve the process and on the role of risk assessment.

EXISTING RISKS IN RECONSTITUTION

Patient risks due to poor reconstitution practices

The preparation of parenteral medicines in healthcare establishments in clinical areas such as wards and operating theatres is a process that carries high risks of microbiological contamination, incorrect product composition and health and safety issues.^{3–7} Errors have been shown to be associated with additional morbidity and mortality in an already critically ill population.⁸ Parenteral medication errors are a serious safety problem and are recognised as a high-priority topic in healthcare establishments.^{9–11} Reconstitution is, therefore, of crucial importance for patient safety.^{12–18}

Type of risks associated with poor reconstitution practices

Reconstitution of parenteral medication may carry the following risks:

► Possible failures in the reconstitution process.

Errors in the reconstitution process for parenteral medicines can occur, resulting in an inadequate medicine to be administered to the patient.¹⁹ Some examples of errors are:

- Reconstitution of the wrong medicine.¹⁵
- Reconstitution of the wrong dose.¹⁵
- Reconstitution of a medicine for the wrong administration route.¹⁵
- Calculation errors leading to administration of the wrong dose and/or at the wrong concentration or rate.¹⁷
- Incorrect reconstitution (insufficient mixing, incomplete dissolution, use of the wrong diluent).¹⁸
- Label content.¹⁷
- Poor aseptic technique (see later).¹⁸
- The failure to have a double check by an independent second person.¹⁶
- Not following the reconstitution instructions given in the SmPC from the manufacturer.¹⁶
- Use of a medicinal product, diluent or infusion after its expiry date (and time if appropriate).¹⁷
- Incompatibility between diluent, infusion, other medicinal products or administration devices.¹⁶
- The reconstitution process is not clearly or not sufficiently described in the SmPC,¹ leading to misinterpretation.¹⁶

► Risk of microbiological contamination.

Many reconstitutions of parenteral medicinal products are carried out in clinical areas, for example, wards, theatres and clinics. It is difficult to achieve true asepsis in these uncontrolled environments. Poor-aseptic (non-touch) technique leading to contamination of the product and harm to the patient is a risk. Therefore, the risk of microbiological contamination of the medicine should be reduced to an absolute minimum during reconstitution.²⁰

The literature indicates that aseptic procedures related to the reconstitution process are often deficient,¹⁸ resulting in a risk that the medicine is microbiologically contaminated. Literature also indicates that the microbiological contamination of syringes reconstituted by intensive care nurses varied from 7% to 44%.²⁰ In a pharmacy with qualified personnel and a controlled environment, these percentages are regularly much lower.²⁰ Fatalities as a consequence of an intravenous anaesthetic contaminated with viruses or bacteria have been reported.²¹ A favourable nutrient medium for microorganisms may be a causative factor for a high number of infectious complications.²² There have also been fatalities with PN.^{23–25}

Reduction of patient risks needed

To reduce patient risks, the option of developing additional guidance for the reconstitution process was considered by the Committee of Experts at the Council of Europe,²⁶ coordinated by the European Directorate for the Quality of Medicines & Healthcare (EDQM, Council of Europe). One of the outcomes of a survey among European countries carried out by this Committee of Experts was that there is no or just limited regulation concerning reconstitution.

PREVIOUS WORK AT THE COUNCIL OF EUROPE

Background to the reconstitution project as a development of previous work

In 2008, a working party of the Committee of Experts chaired by the corresponding author with the participation of the delegations from Austria, Norway and Switzerland sent a survey on quality and safety assurance standards for the preparation of medicinal products to the different countries belonging to the Council of Europe. The fact that the regulations for products manufactured by the pharmaceutical industry and pharmacy-made preparations are not the same gave cause to this survey. The results of this survey have been published.²⁶ The main conclusions of this survey were as follows.

The preparation of medicines in pharmacies and the reconstitution of parenteral medicines are invaluable in accommodating the individual needs and medical conditions of patients in Europe and beyond. The preparation of medicinal products in pharmacies, notably standards for quality assurance and safety, are not harmonised throughout Europe and fall under the national competencies of individual European countries. Following the conclusions of the above survey²⁶ carried out by the Committee of Experts on Quality and Safety Standards for Pharmaceutical Practices and Pharmaceutical Care (Council of Europe) supported by the EDQM, a wide gap was identified between respondent countries in terms of quality assurance and standards for pharmacy-made medicinal products, as well as a gap in quality assurance between preparation in pharmacies and medicines prepared by the pharmaceutical industry. This survey also indicated that there is no or just limited regulation concerning reconstitution. Based on this work,²⁶ further discussions took place among professionals from 21 European countries during an expert workshop.²⁷ This resulted in a Resolution¹ on pharmacy preparation, which included some recommendations and an outlook to further work on reconstitution of parenteral medicines.

Resolution on harmonisation of pharmacy preparation with a paragraph on reconstitution

In December 2010, the Committee of Experts proposed standards for harmonising quality and safety standards for pharmacy preparation of medicinal products in Europe in the form of a draft Resolution, which included a paragraph (paragraph 9) on reconstitution.¹

The Committee of Ministers has now adopted Resolution CM/Res AP(2011)1¹ on quality and safety assurance requirements for medicinal products prepared in pharmacies for the special needs of patients, again with a paragraph on reconstitution. The Committee of Ministers has recommended that member states adapt their legislation in line with the provisions of the above Resolution. The Resolution is a statement of political will, but legally its implementation is not obligatory (in contrast to, eg, an EU Directive) and national frameworks will be taken into account by the member states.

The Resolution¹ is a major breakthrough in preventing quality and safety gaps between medicinal products prepared in pharmacies and in industrial settings by outlining key elements of quality assurance in the preparation processes. The patient has the right to obtain a product that fulfils appropriate quality standards irrespective of where it is made (industry, pharmacy or healthcare establishment). An innovative approach, such as the decision-making aid for determining the required level of quality standards, is included in the Resolution.¹

Implementation of standards established by the Council of Europe for quality assurance and safety of medicines made by preparing pharmacies can prevent serious incidents with such medicines in Europe. Such serious incidents have occurred in other countries outside Europe, notably in the USA.^{28–30}

Reconstitution paragraph in Resolution

In chapter 9 of the Resolution,¹ specific reference is made to the reconstitution of medicinal products in healthcare establishments. It is stated that reconstitution of medicinal products should preferably take place in a pharmacy, assuming that the requirements concerning the safe preparation of sterile products can be fulfilled.

A risk assessment for reconstitution should help the healthcare establishment in deciding and documenting which products should be reconstituted in pharmacies and which products can be reconstituted in clinical areas such as wards, theatres and clinics.

Reconstitution of a medicinal product having a marketing authorisation in order to form a ready-to-administer medicinal product is considered a grey area by the authors of the abridged survey report,²⁶ where further work is needed. The Resolution¹ recommended that national authorities should develop, in cooperation with the relevant professional bodies, specific legislation or guidance taking into consideration the factors stated in chapter 9 of the Resolution.¹ At present, legislation concerning reconstitution of parenteral medicines is missing or insufficient in most of the countries of the Council of Europe.

ONGOING ACTIVITIES CONCERNING RECONSTITUTION AT THE COUNCIL OF EUROPE

Decision to work in the area of reconstitution

Based on the previous research that was undertaken by the Committee of Experts in the area of pharmacy preparation, initiatives were taken in the same committee to work on reconstitution. A project proposal was made, and consensus was reached among the member states of the Council of Europe to initiate this project. Factors such as the different locations for the reconstitution processes, a risk-based approach in the function of the different types of reconstitution processes, the reconstitution services delivered by pharmacy and other managerial matters were to be taken into account.

Focus on the reconstitution process in the different locations of the healthcare establishment

In practice, the reconstitution process may take place in pharmacies as well as in clinical areas. Ideally, the quality of medicines for patients should be independent of the place where the medication is reconstituted. Guidelines for reconstitution have been established in some countries, for example, the UK,³¹ but are needed across Europe. Guidelines should deal with working methods and procedures for reconstitution and administration of parenteral medicines in particular.^{6 32 33}

Resolution highlights structural improvement of reconstitution processes through adequate management of the risks

In each of these locations (pharmacies or clinical areas) in the healthcare establishment, the risk profile may be different, depending on the situation in the location (complexity of the reconstitution process, premises and equipment and provisions, personnel and qualifications, other conditions) as well as the number of operational steps involved in the reconstitution.

Reconstitution is a broad term for different types of activities and services. The risk profiles for these different reconstitution processes may be very different and, therefore, relevant to consider. By using the same term, the implicit, though inadequate, suggestion is that the risk profile for all these different activities is identical.

A risk assessment for reconstitution can help healthcare establishments in deciding and documenting which products should be reconstituted in pharmacies and which products can be safely reconstituted in clinical areas with appropriate risk-reduction measures, for example, training. Risk management of the reconstitution process only reactively on the basis of incidents is an inadequate response. Incident-driven process improvement should, in our opinion, be replaced by proactive structural improvement based on a risk assessment. In our view, this is only possible with the commitment of the board of directors and of the clinical staff in any healthcare establishment. The reconstitution process for parenterals and administration to patients in healthcare establishments has to be based on a thorough risk assessment and good management.

The expert committee is considering some options that are likely to be important to establish good reconstitution practices (GRPs). For example:

- ▶ The nomination of a specific person in the healthcare establishment with appropriate qualifications with overall responsibility for the reconstitution process of parenterals (eg, a hospital pharmacist).
- ▶ An overview within the healthcare establishment of the various reconstitution activities for the different locations (pharmacy, clinical areas), distinguishing the different risks.
- ▶ A hospital-wide assessment on how to deal with these risks.
- ▶ A decision on which products should be prepared in the hospital pharmacy and which products can be reconstituted in the clinical areas.
- ▶ An assessment of the capacity within the hospital pharmacy to provide ready-to-administer parenteral products, targeting high-risk products and to support the education of staff in clinical areas to safely reconstitute products.
- ▶ The engagement and commitment of the board of directors in the healthcare establishment is required to make progress in the area of reconstitution of parenteral medicinal products.

Focus on the reconstitution process not including the last step of administration to the patient

The work of the expert committee focuses on the reconstitution process itself. The last step in the handling of medicinal products is the administration to the patient. Procedures to have an independent check performed by a second employee should be implemented. This independent check should include a check on the patient details, the prescription and the medication to be administered. Errors occurring in the last step, that is, the administration to the patient cannot be corrected at a later stage. Therefore, such errors in administration to the patient can also have a crucial impact on patient safety.

CONCLUSIONS

At present, legislation and/or guidance concerning reconstitution of parenteral medicines are missing or insufficient in most of the countries of the Council of Europe. The Resolution¹ recommends that national authorities should develop, in cooperation with the relevant professional bodies, specific legislation or guidance. In order to facilitate the work in the member states, the Committee of Experts has taken the initiative to develop legislation or guidance at the international level. The work of the Committee of Experts describes and addresses the different risk issues in relation to the reconstitution process and aims to give practical advice on the management of this process. It is expected that the Committee of Experts will produce recommendations for setting up regulation for GRPs. In a voting among the member states of the Council of Europe, the recommendations may be agreed upon. Because there is no or just limited legislation and guidance concerning reconstitution in Europe, such regulation at the level of the Council of Europe would be a major step to increase patient safety in the area of aseptic preparation of medicinal products in healthcare establishments.

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