Pharmacy preparations

Valorisation

Today, the vast majority of medicinal products are prepared industrially. However, medicinal products manufactured by the pharmaceutical industry are not always authorised, or available, to cover the special needs of individual patients. Pharmaceutical companies, and indeed, pharmacies themselves are certainly involved in individual health care. But, in practice, pharmacists are confronted with the special needs of patients for which no licensed industrial product is available on the market. However, society expects the pharmacist to dispense a pharmacy preparation which can meet the special medical needs of individual patients. There are many examples of special patient needs which can be treated with pharmacy preparations, such as the special needs of children and the elderly.

The regulation of the preparation of medicinal products was started on a European level in 1965, three years after the thalidomide tragedy in which thousands of infants of mothers who had used the drug during pregnancy were born with malformed limbs. Arms and legs were either not developed or presented themselves as stumps. Many of these infants did not survive. This tragedy led to the development of more structured drug regulations in order to prevent this from happening again. Since 1965, the European regulation has been built upon two important pillars:

- Product design quality
  Marketing authorisation was now required which has to be issued for each medicinal product by the competent regulatory authority before the product is placed on the market.
- Production quality
  The manufacturer must obtain a manufacturing licence issued by the competent authority. Compliance with Good Manufacturing Practice is obligatory for manufacturers of medicinal products.

There are some exceptions to the European regulation, such as specific pharmacy preparations and medicinal products to meet special medical needs. It is legal for pharmacists to prepare any medicinal product in the pharmacy as long as it falls under the exceptions to the European regulation. If these exceptions are applicable, then any legislation and standards relating to the quality and safety of pharmacy preparations are, in principle, set at the national level.

We have shown in this thesis that today, not every pharmacist in Europe prepares medicines. Instead, there are preparing and distributing pharmacies (PDPs) in many countries to which the pharmacist can outsource pharmacy preparation. These PDPs prepare medicinal products in their pharmacy and distribute these products to dispensing pharmacies.

Some of these PDPs have developed into companies which prepare medicinal products on a large scale, while retaining their formal status as a pharmacy. Preparation on a large scale, however, increases the risks to patient care, for example in

the case of defects in the quality of the product. To contain these risks, stringent quality and safety standards have to be put in place. We have shown that there is a lot of variation in the quality and safety standards applied in Europe. This variation, includes standards for PDPs. This is, for example, the case, when regarding the requirements for production quality. Moreover, standards for product design quality were, apparently, missing in most of the countries.

In addition, we have shown that, based on case law in 2015, there are few legal opportunities for pharmacy preparations and individual health care. The European Court of Justice (ECJ) has provided a strict interpretation of the exceptions to European regulation for pharmacy preparations. This is laid out in Directive 2001/83/EC, in particular with regard to the magistral formulae and the officinal formulae. European regulation applies to all medicinal products prepared industrially or manufactured by a method involving an industrial process (hereafter: industrial and industrial process medicines, IPMs). This is irrespective of whether these products are made by a private company or in a pharmacy. Therefore, the regulation is mandatory for all people and companies preparing IPMs. The exceptions to European regulation apply to small-scale pharmacy preparation, for example the magistral and officinal formulae. Since many pharmacies have become dispensing pharmacies which do not prepare medicinal products, this option of small-scale preparation has been replaced in many countries by preparation through PDPs. These now make medicinal products to satisfy the medical needs of the patients of these dispensing pharmacies. However, the exceptions to European regulation are not applicable to PDPs. PDPs making unlicensed medicines to meet the special medical needs of individual patients belonging to pharmacies, and who do not prepare their own medicinal products, are not recognised as an exception to European regulation. Consequently, this status of the PDPs poses a problem to the individual health care of these patients.

We have shown that many European countries have attempted to find national solutions for PDPs in order to permit individual health care where needed and at the same time to ensure that medicinal products are safe, effective and of high quality. We have shown that, in the Netherlands, the measures taken by the authorities regarding the quality and safety standards are generally accepted and followed by the PDPs. This Dutch regulation requires that pharmacy preparations are only permitted if there is a favourable pharmacotherapeutic rationale and if no licensed pharmacotherapeutical alternative is available on the market. In addition, a product dossier should be available for all products to ensure the product design quality and compliance with Good Manufacturing Practice (GMP) is required to guarantee the production quality. The different national solutions could form a basis for a reform of European regulation.

We have shown that good progress has been made with the implementation of Resolution CM/ResAP(2011)1. This Resolution was confirmed again in 2016. [1]

This means that the harmonisation of quality and safety standards for pharmacy preparations has made good progress in Europe. With regard to production quality, GMP is required in most of the countries for high-risk pharmacy preparations. For PDPs, for example, both the requirements of GMP and that for complying with good distribution practices (GDP) are followed in most countries. We have also shown that, in relation to the product design quality, the concept of product dossiers has either been implemented or implementation is planned for most countries. We have also shown that there is room for improvement in other areas, such as the recommendation included in the Resolution to consider the requirement of a marketing authorisation for specific pharmacy preparations in specific cases.

We conclude that few, or no, quality and safety requirements have been laid down for preparations in clinical areas in health care establishments. We investigated the high risks for patients associated with the reconstitution of parenteral medicines and the immediate harm this can cause to patients. This is, in particular, the case in health care establishments where aseptic preparations are carried out in hospital pharmacies as well as in clinical areas. We defined, in this study, the options for quality and safety standards in relation to the patient risks which were detected. These were in order to ameliorate the process for aseptic preparations in health care establishments for the benefit of the patient. These standards include, for example, the nomination of a designated person in the health care establishment, the laying down of minimum requirements for quality standards in clinical areas to be included in a quality system, and the application of a risk assessment approach as a basis for a decision about which products can be reconstituted safely, in which locations in the health care establishment, and under which conditions.

In our thesis, we have shown that the harmonisation of quality and safety standards in Europe, for all pharmacy preparations, is making good progress. However, now we face another problem, as we have shown in Chapter 4. This is that the legal opportunities for pharmacy preparations have diminished over the years thus hindering the further implementation of the harmonised quality and safety standards of 2011. [1]

We have investigated European legislation for pharmacy preparations and its relationship to the European quality and safety standards of 2011.[1]

European regulation, more specifically Directive 2001/83/EC, is outdated as far as pharmacy preparations are concerned and from the perspective of the patient its reform is needed urgently.

Small-scale preparation of medicinal products is addressed in European regulation and permitted under the competencies of the national authorities. However, this does not offer opportunities for the patient with special medical needs. Today, many pharmacies in Europe have stopped preparing products and have outsourced pharmacy preparations to PDPs which make preparations on a larger

scale. Yet, European regulation was created at a time when every pharmacists made medicinal products for his or her own patients and when large-scale pharmacy preparation did not exist.

The option that pharmacies which do not prepare medicinal products should make use of the services of PDPs would be one possible means to benefit the patient with special needs. However, PDPs may exist in many European countries but they are not addressed in European regulation. It is shown that according to recent case law of the European Court of Justice, the exceptions from European regulation are not applicable to PDPs. In particular the Abcur case has caused a lot of uncertainty among pharmacists in Europe. This uncertainty is based upon concerns that there may no longer be a legal option for PDPs to make preparations on a larger scale – that is aimed at serving the special medical needs of patients. PDPs have to comply with Directive 2001/83/EC and the exceptions for pharmacy preparations do not apply to them.

Our study shows that many European countries try to find national solutions which allow pharmacotherapy to be tailored to the needs of individual patients on the one hand and which ensure that medicines are safe, effective and of high quality on the other. It has been shown that Dutch standards for PDPs have been accepted and that PDPs are capable of complying with adequate quality and safety standards.

The harmonised quality and safety standards for pharmacy preparations of 2011[1] and the different national solutions could serve as a basis for a change in European regulation which is urgently needed from the perspective of the patient.

In the specific area of reconstitution in health care establishments, our research shows that there is little or no regulation in this area in most of the member states of the Council of Europe. The risks associated with the aseptic preparation of parenteral medicinal products in health care establishments, and the options for reducing the patient risks by setting up regulation for Good Reconstitution Practices, have been studied. The 2016 quality and safety standards for good reconstitution practices [2] reduce the risks associated with the reconstitution of parenteral medicines and thus offers an opportunity for improvements in patient safety.

Research calls for more research.

Further research is needed to show how the implementation of the good reconstitution practices of 2016 will develop over time in the different Council of Europe member states.

The implications for further research in the area of pharmacy preparation are also included in this thesis. This research should be aimed at making the best use of the harmonised quality and safety standards and the different national solutions for

the required change in European regulation. Pharmacy preparations aimed at satisfying the medical needs of individual patients need to have a solid legal position in Europe and medicines must be safe, effective and of high quality. This could be achieved by means by setting standards for production quality and product design quality. Future research in the area of pharmacy preparations in Europe should adopt a structured approach in order to coordinate all the efforts aimed at serving the interests of the patient.

There is an urgent need for future research into the areas of pharmacy preparation and preparations in health care establishments. It is essential to make this knowledge available, because society expects the pharmacist to dispense a pharmacy preparation dedicated to the special medical needs of individual patients. Based on his or her expertise in pharmacy preparation, the pharmacist has opportunities to extend this role to the benefit of the patient in health care establishments.

References

1. Resolution CM/Res(2016)1 on quality and safety assurance requirements for medicinal products prepared in pharmacies for the special needs of patients (Succeeding Resolution CM/ResAP(2011)1 on quality and safety assurance requirements for medicinal products prepared in pharmacies for the special needs of patients) (Adopted by the Committee of Ministers on 1 June 2016 at the 1258th meeting of the Ministers' Deputies). Website: https://www.edqm.eu/sites/default/files/resolution_cm_res_2016_1_quality_and_safety_assurance_requirements_for_medicinal_products_prepared_in_pharmacies.pdf
2. Resolution CM/Res(2016)2 on good reconstitution practices in health care establishments for medicinal products for parenteral use. Good reconstitution practices, website: https://search.coe.int/cm/pages/result_details.aspx?objectid=090000168065c135