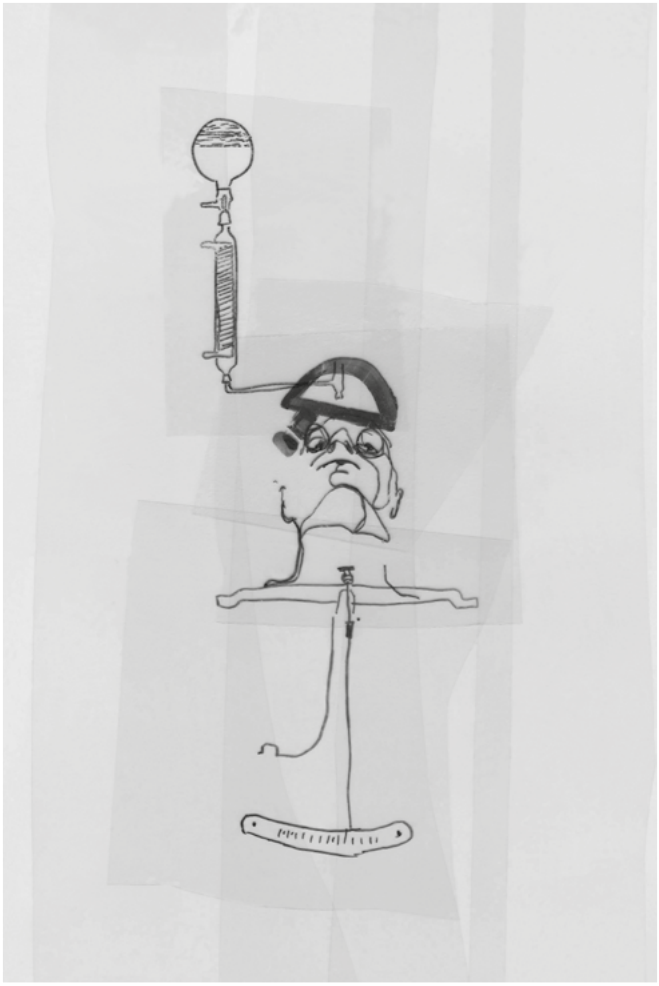
Pharmacy Preparations

European quality standards and regulation



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Pharmacy Preparations

European quality standards and regulation

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Chapter 1

General introduction

The governance and quality of health care

The quality and safety of health care falls under the national competencies of individual European countries. These national authorities should safeguard the interests of patients, in particular when patients are unable to check the quality and safety of health care themselves. A low quality of care can have serious consequences for the health of patients[1].

Individual European countries should fulfil their obligations under international law as far as it is applicable[2,3,4,5]. However, besides the national authorities, different associations of professional bodies and individual health care providers are also responsible for the quality and safety of health care on many different levels. Professionals should adhere to national laws and also, if applicable, to guidelines issued by the professional bodies[6].

The special position of medicinal products within health care

Medicinal products are essential in health care in order to meet the needs of patients. Until approximately 1950, these medicinal products were, in most cases, prepared by pharmacists[7]. There was then a gradual shift in their preparation from the pharmacist towards the pharmaceutical industry[7]. Today, the large majority of medicinal products is prepared industrially, however, pharmacy preparation remains important in order to cover the special individual needs of patients. Examples of these are the need for a product that does not cause an allergic reaction or the need for a product adjusted to an individual dose.

Medicinal products hold a special position within health care as they are subject to additional legislation aimed at safeguarding public health. The international dimension is stronger for medicinal products compared to health services provided by local professionals. This is because regulations, apart from those applying to health care, have to be taken into account. For example regulations concerning the free movement of goods may also apply[8].

European and national legislation for medicinal products

The legislation in the European union (EU) is relatively dominant compared to national legislation with regards to medicinal products prepared industrially or manufactured by a method involving an industrial process (hereafter: industrial and industrial process medicines, IPMs). National authorities are obliged to comply with European regulation. This requires, for example, that all medicinal products are assessed before they are placed on the market and, if applicable, approved by the competent authorities, either at the national or international level. It also means that production must comply with Good Manufacturing Practices (GMP)[9].

Legislation for industrial medicinal products and the requirements of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH)[10] provide a basis to ensure that medicines are safe, effective and of a high quality.

IPMs are, however, not suitable for treating all patients. A relatively small group of patients may have special needs for the treatment of their medical condition, which cannot be fulfilled by these IPMs. For this reason pharmacotherapy tailored to the needs of individual patients is of crucial importance. Pharmacies may therefore receive requests from health care providers to prepare a medicinal product to fulfil the special needs of an individual patient, for which no licensed medicinal product is available on the market.

National legislation for pharmacy preparations for the needs of individual patients

National legislation enjoys a relatively dominant position with regard to medicinal products made in pharmacies. However, national legislation only prevails over EU legislation if the exceptions to EU law apply[11]. The assumption is that, if national legislation prevails, pharmacy preparations may differ between countries with regard to the quality and safety standards.

The preparation of medicinal products in pharmacies within Europe may therefore be less harmonized than for IPMs, in particular with regard to quality and safety standards. However, the patient is entitled to a medicinal product of good quality, irrespective of where the product is made. The patient should be able to trust both the quality of IPMs - but also of those made in a pharmacy.

Medicinal products are essential for individual health care

As medicinal products are essential for individual health care, quality and safety standards are therefore required since they provide a basis for medicines that are safe, effective and of high quality, which is indispensable for treating individual patients.

In Europe, the large majority of medicinal products are IPMs. Legislation and quality and safety standards for these medicinal products are set at the European level[11]. The standards are uniform, unequivocal and based on the following two pillars:

- Product design quality
  Each IPM must obtain marketing authorization issued by the competent regulatory authority before being placed on the market. The registration dossier of the licensed medicinal product contains all the technical data, such as administrative, quality, non-clinical and clinical data.

- Production quality.
  The manufacturer should hold a manufacturing license issued by the competent authority. This license is dependent on compliance with Good Manufacturing Practices (GMP).

Pharmacy preparations

This thesis is about pharmacy preparations. Products made in a pharmacy are needed for a relatively small group of patients. These are those with special needs for the treatment of their medical condition in cases where IPMs are either not available on the market or not suitable for their treatment.

In almost all cases these medicinal products prepared in pharmacies have not obtained a marketing authorization. Medicinal products made in a pharmacy are unlicensed. Legislation and quality and safety standards for pharmacy preparations are in principle set at the national level:

- Product design quality and production quality.
  Pharmacists can legally prepare any medicinal product in their pharmacy by virtue of their professional education, professional license and the licensing of the pharmacy's premises. The assumption is that uniform standards based on the two pillars of product design quality and production quality, and which are applicable for IPMs, may not exist.

Pharmacy preparations can be subdivided into:

- magistral formula[12]: Any medicinal product prepared in a pharmacy in accordance with a medical prescription for an individual patient.
- officinal formula[13]: Any medicinal product which is prepared in a pharmacy in accordance with the prescriptions of a pharmacopoeia and which is intended to be supplied directly to the patients served by the pharmacy in question.

Today, some countries have Preparing and Distributing Pharmacies (PDPs), which prepare medicinal products at the request of another pharmacy. PDPs prepare medicinal products in their pharmacy and distribute these products to a dispensing pharmacy, thereby acting as if they are not pharmacies but pharmaceutical companies. The dispensing pharmacy receives the prescription for a patient and provides the pharmacy preparation, made by another pharmacy, to the patient. But it is unclear which regulation covers these PDPs and what quality and safety standards apply.

In this thesis, attention is also paid to the reconstitution of parenteral medicines, which cannot be seen either as a regular pharmacy preparation or as industrial manufacture. This is because the starting material is a licensed medicinal product instead of raw material described in a pharmacopoeia monograph. A second rea-

son is that the preparation often occurs in the clinical areas of health care establishments instead of pharmacies. Reconstitution is defined as: manipulation enabling the use or application of a medicinal product with a marketing authorization in accordance with the instructions given in the summary of product characteristics or the patient information leaflet[14].

The Council of Europe and one of its Committee of Experts

The Council of Europe (CoE) and the European Union (EU) share the same fundamental values of human rights, democracy and the rule of law. However, they are separate entities which perform different, yet complementary roles. The EU often builds upon CoE standards when drawing up legal instruments and agreements which apply to its 28 member states. Furthermore, the EU regularly refers to CoE standards and monitoring work in its dealings with neighbouring countries, many of which are members of the CoE[15].

The Committee of Experts on Quality and Safety Standards in Pharmaceutical Practices and Pharmaceutical Care (CD-P-PH/PC) at the CoE - hereafter known here as the Committee of Experts - supported by the European Directorate for the Quality of Medicines & Healthcare (EDQM), is doing substantial work in the area of pharmacy preparation. European countries have nominated delegates to participate in this Committee of Experts working on different subjects such as the quality and safety standards for pharmacy preparations.

The mandate of the Committee of Experts is based upon its terms of reference established by the Committee of Ministers under Article 17 of the Statute of the Council of Europe. This is in accordance with Resolution CM/Res(2011)24[16] on inter-governmental committees and subordinate bodies, their terms of reference and working methods. This mandate of the Committee of Experts is renewed every two years.

Not all member states of the Council of Europe are involved in its work on pharmacy preparations. It is only the member states which signed the Convention on the Elaboration of a European Pharmacopoeia who have participated (Ph. Eur. member states).

The Committee of Experts holds regular meetings and carries out its programme of activities using scientific and public health orientated approaches. It also makes use of a structured and systematic approach to its work on proposals for new areas of interest and for carrying out its regular activities. It achieves its aims through arranging consultations, hearings, conferences and seminars.

The Committee of Experts has chosen to take the initiative in its work on pharmacy preparations. The challenge here is the assumption that there is a contrast with the

quality and safety standards for medicinal products made in the industry and the assumption of the diversity of national quality and safety standards and regulations for products made in a pharmacy. The work was considered to be in the interest of the patient because he or she is entitled to a medicinal product of good quality and safety, irrespective of where the product is made. Moreover, the assumption that there is a problem in the divergence in the quality and safety standards for medicines made in a pharmacy in the member states - and its pharmaceutical and legal consequences - has not been addressed in academic literature.

The aims of this thesis

This thesis concerns research into the quality and safety standards in pharmacies and healthcare establishments. This research is conducted at the level of the member states of the CoE who signed the Convention on the Elaboration of a European Pharmacopoeia (Ph. Eur. member states). The information was gathered at the level of the delegates of the different member states. These delegates are supposed to liaise with different stakeholders in their country before taking a position. Different methods were used in this thesis, but detailed investigations at the level of each member state were, in general, outside of its scope.

Two Dutch studies as regards PDPs were, however, included in the research, because they show the crucial importance of not only quality and safety standards, but also of the regulations for the healthcare of patients and, in particular, patients with special medical needs.

EU legislation relating to medicinal products was studied because this plays a dominant role in the production of IPMs - medicinal products prepared industrially or manufactured by a method involving an industrial process. IPMs are usually made in the pharmaceutical industry, but also certain PDPs may produce them. A study was performed into the demarcation line between pharmacy preparations, where national legislation prevails because they are outside the scope of EU regulation, and pharmacy preparations, where the EU regulation applies.

The term regulation in this thesis is used as a general term for different types of legislation and standards. Where confusion could arise, an explanation will be given for what is meant. Listed here are the types of regulation with the most legally binding placed first:

- A Regulation, for example Regulation (EC) No 726/2004, is a type of EU regulation that is directly legally binding on all EU countries. A Regulation does not need to be implemented into national legislation.
- A Directive, for example Directive 2001/83/EU, is a type of EU regulation that is not directly legally binding on all EU member states, but needs to be imple-

mented into the national legislation of the various EU countries. Directives may leave room for different options or some deviations at the national level.

- A CoE Resolution is an expression of political will of the member states of the Council of Europe. It is based on a consensus of the member states concerning a topic, for example pharmacy preparations or good reconstitution practices. A CoE Resolution is regularly used by the CoE member states or the EU to serve as a basis for, or input to, new regulations or legislation.
- A professional standard, for example the guidelines of professional associations[6].

The aims of this thesis are :

- to study and evaluate relevant quality and safety standards for pharmacy preparations in a selection of the member states of the Council of Europe, before harmonizing these standards (chapter 2).
- to study and evaluate in a selection of the member states of the Council of Europe the steps taken at the Council of Europe towards harmonization of the quality and safety standards for pharmacy preparation in its member states (chapter 3).
- to study and evaluate the legislation for the preparation of medicinal products in the EU and the balance between EU and national competencies (chapter 4).
- to study the risks associated with the reconstitution of parenteral medicinal products in health care establishments and to evaluate possible options to establish appropriate quality and safety standards at the level of the member states of the Council of Europe (chapter 5).
- to study the relevant quality and safety standards for PDPs in the Netherlands and its compliance (chapters 6 and 7).

The outline of this thesis

Chapter 2 shows the results of a survey on quality and safety standards for pharmacy-made medicines in a selection of the member states of the Council of Europe. This survey investigated the differences concerning these standards and looked at possible gaps with regards to the pharmaceutical industry's standards. In this survey the legal provisions and definitions, the standards for pharmacy preparation and the provisions and practices for preparation and delivery between pharmacies were studied.

In particular, the following elements were studied: the restrictions at the national level related to the preparation of medicines in pharmacies; the authorization of pharmacies and possible additional authorizations; the additional standards for preparations carrying a higher risk; the clinical relevance and added value of the

pharmacy preparations; the testing of raw materials, pharmacovigilance and specifically the national registries for adverse events; a possible marketing authorization for pharmacy-made products; trade in pharmacy-made medicines; and, centralization trends.

Moreover, the regulations and standards for reconstituted products were studied. Product quality itself was not assessed, but the existence was studied in the different countries of official medicines control laboratories which take care of the surveillance of the product quality.

In C*hapter 3*, the quality and safety standards for pharmacy preparation developed at the Council of Europe are presented. An investigation is carried in a selection of the member states of the Council of Europe to assess the progress in the implementation of these standards in the national legislation of its member states.

Chapter 4 reports the results of a study about the legislation for medicinal products in Europe and the accompanying quality and safety standards. Circumstances in which the EU regulation does not apply are investigated. It gives insight into the recent interpretation of the European Court of Justice (ECJ) concerning the scope of EU legislation for medicinal products and the exceptions to it where national legislation can be applied.

In C*hapter 5*, the risks associated with reconstitution of parenteral medicinal products in health care establishments were studied. Errors in the preparation of these medicines or inappropriate aseptic procedures may lead to a product which can cause immediate harm to patients. Aseptic preparation of medicinal products is carried out in hospital pharmacies as well as in clinical areas in health care establishments. Options to establish good reconstitution practices are studied.

In C*hapter 6*, Dutch Preparing and Distributing Pharmacies (PDPs) are studied. The Medicines Act in the Netherlands is based on European Union (EU) Directive 2001/83/EC which forbids a PDP from preparing and distributing an unlicensed medicinal product to a dispensing pharmacy that will, in turn, dispense the product to the patient. In order not to obstruct patient care, the Dutch Inspectorate has sent a Circular on large-scale preparation to all Dutch pharmacists. The compliance of the PDPs with the conditions of the Circular are studied.

In C*hapter 7*, compliance with two specific conditions of the Circular were studied. These conditions are that the PDPs perform verifiable investigations to assess the availability or not of licensed pharmacotherapeutical alternatives and to assess the pharmacotherapeutical rationale and the need for the patient.

In Chapter 8, the main findings of the studies in this thesis are discussed. Recommendations for future research are given.

H. Scheepers has written this thesis in his personal capacity.

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7 Patient needs and the marketing authorisation for medicinal products: an analysis of EU law; Joris Langedijk (J.Langedijk@uu.nl), Henk Scheepers (hp.scheepers@igz.nl), Diederick S. Slijkerman (D.Slijkerman@cbg-meb.nl), Aukje K. Mantel-Teeuwisse (A.K.Mantel@uu.nl), Hubert G.M. Leufkens (HG.Leufkens@cbg-meb.nl), Rob J.G.M. Widdershoven (R.J.G.M.Widdershoven@uu.nl), Marie-Hélène D.B. Schutjens (M.D.B.Schutjens@uu.nl) [in press]

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http://eur-lex.europa.eu/legal-content/NL/ALL/?uri=CELEX:32001L0083
Preamble number 14 and article 81

9 Practices as specified in European Commission Directive 2003/94/EC and EudraLex, Volume 4, on guidelines for good manufacturing practices for medicines for human use.

10 ICH Guidelines
http://www.ich.org/products/guidelines.html

11 Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use
http://eur-lex.europa.eu/legal-content/NL/ALL/?uri=CELEX:32001L0083

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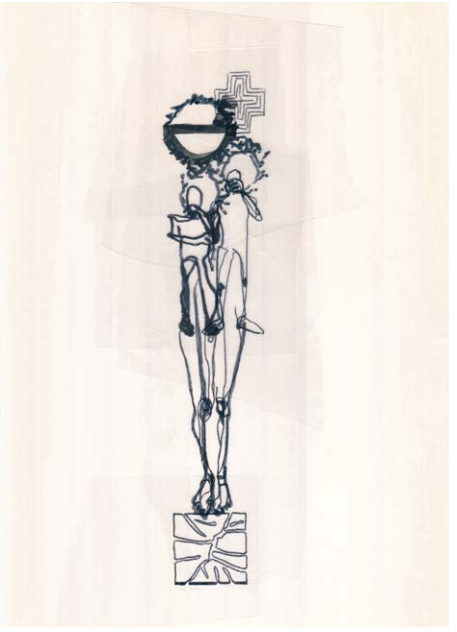

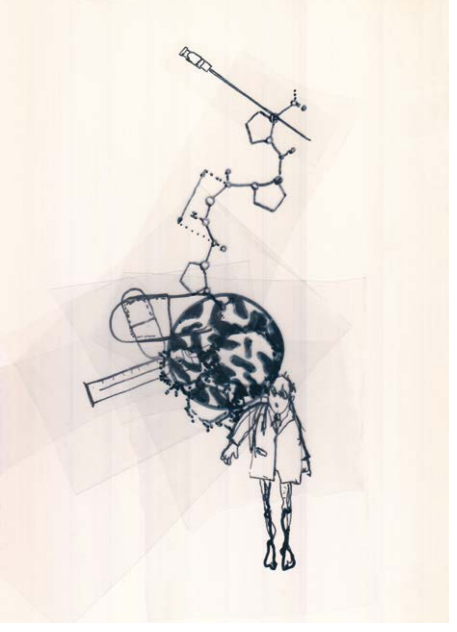

Chapter 2

Pharmaceuticals and pharmaceutical care
Abridged survey report on quality and safety assurance standards for the preparation of medicinal products in pharmacies

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1. INTRODUCTION

The preparation of medicinal products in pharmacies is important because industrial products with marketing authorisations cannot satisfy all the health needs of patients. The regulations for products manufactured by the pharmaceutical industry and pharmacy-made preparations are not the same. This is why the Committee of Experts on Quality and Safety Standards for Pharmaceutical Practices and Pharmaceutical Care (CD-P-PH/PC), coordinated by the European Directorate for the Quality of Medicines & HealthCare (EDQM), Council of Europe), started working on the harmonisation of quality and safety assurance standards for pharmacy-made medicines in Europe. The activity was inspired by the results of a survey on quality and safety standards for pharmacy-made medicines in the states parties to the Convention on the Elaboration of a European Pharmacopoeia. This report describes the survey results.

2. METHOD

The questionnaire for the survey (Appendix) was prepared by a working party of the CD-P-PH/PC chaired by the corresponding author with the participation of the delegations from Austria, Norway and Switzerland. The European Association of Hospital Pharmacists (EAHP) also participated in the work. The questionnaire was divided into four chapters, as follows:

- Legal provisions and definitions;
- General safety and quality systems;
- Provisions and practices for preparation and delivery (supply) between pharmacies;
- Quality and safety of pharmacy preparations

The questionnaire was sent to the states parties of the Convention on the elaboration of a European Pharmacopoeia at expert level, the delegations of the CD-P-PH/PC on 15 September 2008, and at the level of the delegations of the steering body, the European Committee on Pharmaceuticals and Pharmaceutical Care (CD-P-PH) (Partial Agreement) on 6 April 2009.

3. RESULTS

The delegations of 19 countries completed the questionnaire. These countries are: Austria, Belgium, Bosnia and Herzegovina: Federation of Bosnia-Herzegovina and Republica Srpska, Cyprus, the Czech Republic, Denmark, Finland, France, Hungary,

Ireland, Italy, Latvia, Macedonia, the Netherlands, Norway, Poland, Portugal, and Switzerland.

The delegation from the United Kingdom referred to the Medicines and Healthcare products Regulatory Agency (MHRA) Guidance Note No. 14, revised January 2008, entitled *The Supply of Unlicensed Relevant Medicinal Products for Individual Patients*. The manufacturer or assembler of "specials" must hold a Manufacturer's "Specials" Licence granted by the Licensing Authority. The manufacturing/assembly site and its operations are inspected for compliance with Good Manufacturing Practice (GMP) and the relevant regulatory provisions. Export from the United Kingdom to other EU/EEA member states of unlicensed relevant medicinal products may take place under certain conditions.

It should be noted that the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) Guide has another scope and focus: the PIC/S Expert Circle on Hospital pharmacy has recently issued the guide to good practices to the preparation of medicines in healthcare establishments, PE 010-3, 1 October 2008, containing the basic quality related requirements for the preparation of medicinal products normally performed by healthcare establishments and pharmacies for direct supply to their own patients. Concerning this guide the following remarks are relevant:

- the guide does not contain specific requirements for pharmacies preparing on a larger scale and delivering to other pharmacies;
- national legislation and regulatory policies laid down by the relevant competent authority should always be referred to when determining the extent to which the provisions laid down in this guide are binding/applicable[1].

3.1 Legal provisions and definitions

3.1.1 Requirements for preparation in pharmacies and other healthcare establishments

In 16 of the 19 respondent countries, general quality and safety requirements are in place for preparation of medicines in pharmacies such as the general chapters and monographs of the European Pharmacopoeia. In some respondent countries more specific additional requirements are defined (e.g. for the preparation of sterile products; exemption only for 'own formula' preparation).

As regards the preparation in other healthcare establishments (e.g. wards in hospitals), general quality and safety requirements are only present in 8 of the 19 respondent countries. There seems to be a discrepancy between the regulations in pharmacies and in other healthcare establishments, respectively. Reconstitution or

[1] Link: http://www.picscheme.org/publication.php (go to 'documents for inspectors')

extemporaneous blend in hospital wards of industrial medicinal products with a marketing authorisation falls under the definition of preparation in some respondent countries, but does not fall under this definition in other respondent countries.

Excerpts from survey replies:

"Healthcare establishments are allowed to prepare medicinal products for immediate use or for use within a few hours after preparation without possessing a special licence. These preparations are poorly regulated, but the products still have to fulfil the requirements laid down in the European Pharmacopoeia. There is an old regulation dating from 1971 on hygiene which we consider outdated. The national medicines agency is now looking to harmonise this regulation among pharmacies and healthcare establishments".

"Specific types of medicinal products prepared for 'own patients' are exempted from the need to have a marketing authorisation".

"The maximum allowed quantity given in a national ordinance on simplified marketing authorisation is 1 000 packs, which includes a maximum of 30 000 daily doses per year except for hospitals. Hospitals can prepare up to 90 000 individual doses per year. Revision of these quantities is being discussed".

3.1.2 Restrictions related to the preparation of medicines in pharmacies

In some respondent countries there are restrictions concerning the preparation of medicines in pharmacies, whereas in others no restrictions are put in place. Restrictions relate to the scale of the preparations, implying that preparations should be limited to individual patients or to stock preparations reserved for supply to the patients served by that pharmacy. In 12 of the 19 respondent countries a license for pharmacy-made medicines is not required, though some others do require such a license. The license system may discriminate between presentation forms (e.g. specific licenses for sterile products, liquids or tablets, respectively), may concern enterprises which are not pharmacies themselves and may be dependent on the production scale.

Excerpt from survey replies:

"All pharmacies must be registered, but once registered they are entitled to prepare medicinal products".

"A differentiated licensing system is in place for pharmacies specialised in liquids, tablets and sterile products".

"A special licence is required for activities in pharmacy-made preparations. Contracted manufacturers for pharmacies, which are not themselves pharmacies, and, which are not allowed to supply patients directly, require a specific national license from the national medicines agency".

3.1.3 Definitions for pharmacy preparations

The definitions used for pharmacy preparations vary widely between respondent countries. The terms magistral and officinal preparation are used in 14 of the 19 respondent countries, but are obviously not clear enough to distinguish between the different forms of preparations. In most respondent countries the need is felt to indicate the degree of standardisation of the preparation (standardised *versus* non-standardised), the stock size (small *versus* large batch), the use of raw materials or marketed medicines or pharmacopoeial *versus* own formulation, etc. Reconstitution or blend of authorised medicinal products is considered a grey area as to whether it falls under the definition of preparation or not. In some countries like France it is forbidden.

Many respondent countries have indicated that other terms are being used for pharmacy-made preparations, such as: "...hospital preparations..."; "...individual preparations and large batch preparations..."; "...own formula[2]..."; "...extemporaneous or small stock..."; "...stock preparations (standardised), individually standardised preparations, individually non-standardised preparations, extemporaneous preparations in hospital wards, preparations from raw materials, preparations to modify already marketed medicines"; "...bulk intermediate products, batch production, hospital pharmacies, pharmacy-prepared brand medicines..."; "...galenic drugs (stock preparations for own patients), herbal drugs, herbal substances, traditional drugs..."; "...extemporaneous compounding...".

3.1.4 Delivery to other pharmacies

In 13 of the 19 respondent countries there are pharmacies that deliver medicinal products to other pharmacies. In some of these respondent countries companies specialised in the preparation of medicines, but which are not pharmacies, are licensed. Concerning the specialisation in the preparation of medicines, hospital pharmacies are more often involved than community pharmacies.

> *Excerpt from survey replies:*
>
> *"There are companies, not being pharmacies, which possess a licence to manufacture medicines on behalf of pharmacies. According to the pharmacy act, most of the manufacturing should be executed by such companies...".*

3.1.5 Authorisation of pharmacies

In 15 of the 19 respondent countries no special authorisations are required for pharmacies other than the 'normal' authorisation for a pharmacy by the authorities, which automatically includes permission to produce pharmacy preparations. In the remaining respondent countries, a license for pharmacy preparations is required.

[2] not from national pharmacopoeia

Excerpt from survey replies:

"Special authorisation to prepare pharmacy-made medicines is not currently required. However, the Pharmaceutical Practice Bill is in process and it will include such a requirement. This bill will require that pharmacies with laboratories making galenic preparations for other pharmacies must comply with GMP when preparing small quantities".

3.2 General safety and quality standards

In 17 of the 19 respondent countries there are general safety and quality standards for pharmacy preparations. In most respondent countries, the typical GMP chapters are covered in the quality and safety standards, but to a varying extent. Quality control is included in the standards in the majority but not all of the respondent countries. Even when included, quality control is in most cases performed by external bodies and not for all preparations. Provisions for product recall are not included in the standards of all respondent countries. Although these standards are specifically aimed at pharmacies which prepare medicines exclusively for their own patients, a clear distinction with preparations on a larger scale is not made in most of the respondent countries.

Excerpt from survey replies:

"Pharmacies must comply with the good practices for preparations set by the national medicines agency".

"Products must comply with the national or European Pharmacopoeia. The European Pharmacopoeia has supremacy".

3.2.1 Additional standards for preparations carrying a higher risk

In 7 of the 19 of the respondent countries additional safety and quality standards are required for preparing larger batches. However, the definitions for a large batch vary widely from country to country. In some respondent countries a stock preparation is considered a large batch, even when the supply of the prepared medicines is restricted to the patients of the pharmacy in question. In one of the respondent countries the standards state specifically that the existence of adequate premises is required for large-scale production.

Excerpt from survey replies:

"The maximum production permitted for small-scale preparations is set at 300 units per galenical lot".

"Preparation for stock building is considered as a larger batch".

"The Professional Standard states that large batch production should only be carried out in appropriate premises licensed to manufacture medicinal products. Stock preparation is considered as a larger batch".

"AMBO 2009 applicable to industry is also applicable to pharmacies supplying medicinal products to other pharmacies, hospitals etc. and when the usual frequency and amount is exceeded".

"No exact definition exists for a larger batch; the additional standards are applied to all stock preparations".

"A preparation is considered as a larger batch if more than 10 units are produced. Stock preparation is considered as a larger batch" .

In 12 of the 19 of the respondent countries additional safety and quality standards are in place for delivery to other pharmacies, whereas in the remaining respondent countries there are no such additional standards. In some of the respondent countries the delivery of medicines to other pharmacies is legally forbidden, whereas in some other respondent countries it is restricted to very specific cases, where the preparation is in the clear interest of health care. In one of the respondent countries delivery of medicines to other pharmacies is not allowed without a marketing authorisation.

Excerpt from survey replies:

"Pharmacies must comply with the good practices for preparations set by the national medicines agency".

"Delivery to other pharmacies is not allowed without having a marketing authorisation for the medicinal product".

"AMBO 2009 applicable to the industry is also applicable to pharmacies when medicinal products are supplied to other pharmacies, hospitals etc. and when the usual frequency and amount is exceeded".

"Delivery to other pharmacies is not allowed".

"Delivery to other pharmacies is not allowed unless certain requirements are fulfilled".

"Regulation 6 of the Regulation of Retail Pharmacy Businesses Regulations 2008 which were commenced on 29 November 2008 place restrictions on the sourcing of medicinal products by registered pharmacies. Pharmacies are now only entitled to source medicines from persons with manufacturing or wholesaling authorisations or from another pharmacy only to meet the immediate prescription need of a patient. This will have the effect of preventing practices of delivery of medicines from one pharmacy to another except in very specific, and upon occasional, circumstances".

3.2.2 Clinical relevance and added value of the pharmacy preparation

Justification of therapeutic benefit/risk of the pharmacy preparation is included in the quality and safety standards in 4 of the 19 respondent countries.

There are respondent countries where pharmacy-made medicines are not allowed if authorised medicines as therapeutic alternatives are available on the market. In one of the other respondent countries pharmacies are obliged to deliver all medicines prescribed by doctors, whereas another country requires a sound and documented proof for the therapeutic rationale of the prepared medicine.

Excerpt from survey replies:

"Therapeutical rationale has to be demonstrated by the pharmacy in accordance with a classification scheme (e.g. an individual choice of a doctor versus proof by means of clinical trials)".

"Production is according to prescription or good therapeutic tradition. Pharmacies are obliged in our country to deliver all medicines that doctors or veterinarians prescribe".

3.2.3 Testing of raw materials

Determination and testing of the identity of the raw materials is required in 12 of the 19 respondent countries, and further analysis is required in 8 of the 19 respondent countries. In some respondent countries an authorisation system, organised by the pharmacists and based on audits of the suppliers, is in place for suppliers/manufacturers of raw materials, allowing the pharmacist to rely upon a certificate in the case of an 'approved' supplier/manufacturer.

Excerpt from survey replies:

"Pharmacies are required to use pharmaceutical grade raw materials where possible. However, no further specifications are mandated at present".

"Possibility of certification of the identity of individual containers is possible under specific condition for explicitly authorised raw material suppliers or manufacturers".

"In practice, pharmacies can rely on the identity guarantee given by the supplier. A special laboratory tests almost all raw materials for pharmacies".

"A content and/or purity assay etc. is required to be performed if the certificate of suitability of the relevant pharmacopoeia monograph is not provided by the source from which the substance is purchased".

3.2.4 Pharmacovigilance

In 9 of the 19 of the respondent countries pharmacy-made medicinal products are subjected to the pharmacovigilance system for medicinal products, but in the remaining respondent countries this is not the case. In the respondent countries where no exceptions are made for pharmacy-made medicinal products, the national registries for adverse drug events are not always specific enough for pharmacy-made medicinal products in the sense that reporting on the generic name and /or name of the raw materials is difficult or even impossible.

> *Excerpt from survey replies:*
>
> *"Pharmacy-made preparations are subjected to the same pharmacovigilance system as medicinal products prepared by industry".*
>
> *"As medicinal products, extemporaneous products are subject to the same requirements in terms of the reporting of adverse events and pharmacovigilance monitoring. There is no specific system in place for monitoring pharmacovigilance issues associated with extemporaneously prepared products".*
>
> *"According to Article 67 of the Law on medicinal products and medical devices the manufacture of galenic preparations produced in a galenic laboratory of an authorised pharmacy for up to 100 finished packages per day shall not be considered as a manufacturer of medicinal products. Therefore, a pharmacovigilance system is not required".*
>
> *"Adverse effects to drugs should be reported to the national medicines agency. The national register allows for reporting of adverse effects on the generic name and/or the name of the raw materials being used".*

3.2.5 Marketing authorisation

In 17 of the 19 respondent countries a marketing authorisation is not required for medicinal products prepared in pharmacies. In one country a marketing authorisation is only required for pharmacy-made branded medicinal products, whereas in another country a marketing authorisation is required if the maximal quantity for pharmacy-made medicinal products is exceeded. The number of marketing authorisations for pharmacy-made medicinal products varies from 0 to more than 100, depending on the country.

3.3 Provisions and practices for preparation and delivery (supply) between pharmacies

3.3.1 Trade in pharmacy-made medicines

Pharmacies which trade own pharmacy-made medicinal products to other pharmacies exist in 9 of the 19 of the respondent countries. In 14 of the 19 respondent

countries trade in pharmacy-made medicinal products between pharmacies is regulated by the national legislation. In 8 of the 19 respondent countries trade is not allowed unless specific conditions are met (e.g. marketing authorisation; absence of registered alternatives on the market; availability of product dossiers; documented evidence concerning the therapeutic relevance; and GMP). In one country trade is restricted to very specific and occasional circumstances. In 6 respondent countries a license is required for the pharmacy. One country does not differentiate between different kinds of medicinal products regarding trade between pharmacies.

The requirements for pharmacies which trade pharmacy-made medicinal products to other pharmacies may differ from country to country. Some respondent countries require a license (based on GMP or GMP-like conditions and/or Good Distribution Practices (GDP) for such pharmacies. In some respondent countries there is a requirement for the absence of an equivalent medicinal product with marketing authorisation on the market. In two respondent countries chemical, pharmaceutical and microbiological (for sterile/aseptic preparations) data, comparable to the data in a registration dossier, should be available in the pharmacy upon request of the authorities.

> *Excerpt from survey replies:*
>
> *"The regulatory provisions of contained in the national acts on pharmacies are being adopted. They aim to provide greater safety guarantees to patients who consume pharmacy-made preparations. To guarantee the quality of preparations, these provisions establish the conditions for issuing, by the State representative in the department, authorisation for a pharmacy to work as a subcontractor".*
>
> *"Trade is not allowed in our country".*
>
> *"Trade is not permitted. No trade or wholesale distribution of such preparations is allowed without marketing authorisation".*
>
> *"Trade in pharmacy-made preparation is not permitted. Only retail sale is allowed".*

3.3.2 Centralisation trends

Most respondent countries found it difficult to identify a trend concerning the number of pharmacies that trade own pharmacy-made medicinal products to other pharmacies.

In some respondent countries there are enterprises (so called chains) on the market, which own a number of pharmacies. It seems that these chains do not want to have production in all of their pharmacies.

In some respondent countries legislation allows pharmacies to a larger extent than before to buy pharmacy-made preparations instead of preparing them in their own pharmacy.

In some other respondent countries the requirements for pharmacy-made medicinal products are reinforced, leading to a possible "shake out" of pharmacies, which are not able to meet the requirements. Pharmacies may give the following reasons for not being able to comply with the requirements when preparing medicinal products: the level of education of personnel, equipment and premises and new regulations. The consequences for the pharmacy may be either to close down or to stop with the preparation of medicines and to buy these medicines form other pharmacies. In the case that pharmacies are obliged by law to prepare all medicines themselves whereas they are not able to comply with quality standards, harmful consequences for the patient cannot be excluded.

These developments may lead to more centralisation/specialisation of pharmacies with regard to the preparation of medicinal products and also to a decrease in the number of pharmacies involved in preparation of medicinal products.

> *Excerpt from survey replies:*
>
> *"New pharmacy chains owners do not want to have production in all of their outlets. The new pharmacy act allows, to a larger extent than before, pharmacies to buy pharmacy-made preparations instead of preparing them themselves. Centralisation with fewer pharmacies and/or companies offering this service is expected".*
>
> *"As the new Regulation of Retail Pharmacy Businesses Regulations 2008 introduced recently places new restrictions on the sourcing of medicinal products by registered pharmacies, it is envisaged that this practice should decrease. However, it is difficult to estimate the impact on the "trade" of pharmacy-made preparations between hospitals treating inpatients".*

3.3.3 Products with marketing authorisation

The number of pharmacy-made medicinal products with a marketing authorisation issued by their national drug regulatory authority differs from country to country. In 10 of the 19 respondent countries no marketing authorisations are issued for pharmacy-made medicinal products, whereas 4 other respondent countries did not provide information on this matter. In one of the respondent countries new regulations are underway, and it is not envisaged to have marketing authorisations for these preparations. In 13 of the 19 respondent countries the number of pharmacy-made medicinal products with a marketing authorisation is between 0 and 10. In two respondent countries the number of marketing authorisations for pharmacy-made medicinal products is higher than 100.

3.4 Quality and safety of pharmacy preparations

Objective data

In 8 of the 19 respondent countries there are data from national surveillance authorities and/or independent academic institutions on the quality and safety of the pharmacy preparations. In some respondent countries there are official medicines control laboratories which take care of the surveillance of the product quality. These laboratories sometimes perform analyses upon request of the pharmacies and very often only a limited number of products are assessed. Information on the preparation process, e.g. incorporation of quality into the end product by means of quality systems (like GMP in the industry) is missing in most respondent countries. In one of the respondent countries a recent study shows that there are shortcomings, especially concerning batch documentation, labelling and the assessment of therapeutic value of the medicinal product/pharmacy preparation. The authors of the study suggest that the same requirements should apply to pharmacies that prepare medicinal products on a semi-industrial scale as to pharmaceutical manufacturers (industry).

> *Excerpt from survey replies:*
>
> *"A national survey was conducted in 300 pharmacies by inspectors. The results obtained were submitted to the national authorities from February to May 2007. The national synthesis of the Public Health Department specifies the main pharmacy-made preparations (paediatric, geriatric, slimming and magistral preparations made on a small scale based on DHEA) and the conditions for their realisation (i.e. premises, equipment, control system and quality assurance). The national medicines agency has analysed 900 prescriptions. Preparations containing forbidden substances have not been identified. The provision prohibiting the inclusion in the same preparation of poisonous substances belonging to different groups (diuretics, psychotropic anorectics...) is respected. Several points need to be improved. In particular, the need to develop documentation, the generalisation of a quality assurance system and further formalisation of registration operations outsourcing to obtain better traceability was mentioned".*

4. CONCLUSIONS

The results show that there is a wide variety between respondent countries in quality assurance and standards for pharmacy-made medicinal products. There is a gap in quality assurance between preparation in pharmacies and manufacture at the industry level. The terminology used for pharmacy-made medicinal products varies greatly between the member states. There is also a quality and safety gap

between medicinal products prepared in pharmacies and in hospital wards, respectively. In most countries even fewer quality and safety requirements are defined for preparations in hospital wards.

The CD-P-PH/PC discussed the survey results at a workshop with experts from the health authorities and from the field in order to identify criteria and key elements of standards for the quality and safety assurance of medicinal products prepared in pharmacies in Europe, taking into account existing quality guidelines, and new trends and possible issues in the fields of preparation and distribution which were not covered by current legal provisions and guidance documents. Taking account of the debates held at the above workshop the CD-P-PH/PC requested proposals on guidelines for quality and safety standards for pharmacy-prepared medicines with a view to recommending them to the superior bodies of the Council of Europe and its EDQM.

The proposed guidelines for quality and safety assurance for pharmacy-made medicinal products will comprise criteria for evaluating the added value of pharmacy preparation; responsibilities of healthcare professionals, preparation process, product dossier, compliance with pharmacopoeial requirements, reconstitution of medicinal product, authorisation for pharmacies or licenses for companies making preparations for pharmacies, transparency and safety, communication and information to patients, and distribution of pharmacy-preparations.

Guidelines (manufacturing) structures and procedures, documentation, stressing also the needs to apply where possible international standards (WHO, Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) the European Pharmacopoeia. In case a pharmacy-preparation is needed and if applicable, a standard formula should be searched in a national pharmacopoeia or nationally recognised formularies. Active substances and excipients used for the pharmacy-preparations, dosage forms and containers must comply with the relevant chapters and monographs of the European Pharmacopoeia or in absence thereof, of a national pharmacopoeia of a State Party of the Convention on the Elaboration of a European Pharmacopoeia.

The guidelines should be complementary to the current and ongoing works by the European Pharmacopoeia Commission and the European Network on Official Control Laboratories (OMCL) coordinated by the EDQM.

Appendix

Questionnaire on quality and safety standards for pharmacy preparations

I. Legal Provisions and Definitions

1. Do your national regulations include requirements for preparations of medicinal products in
   - o Pharmacies: YES/NO/DO NOT KNOW
   - o If yes, please describe requirements (enclose document or web link): ……...
   - o Other healthcare establishments: YES/NO/DO NOT KNOW
   - o If yes, please describe requirements (enclose document or web link):
   - o ……

2. Do your national regulations include the following restrictions
   - o Preparation is only allowed for an individual patient: YES/ NO
   - o Preparation of medicinal products in a pharmacy, including preparation on stock, is only permitted if the products are supplied to the patient(s) served by that pharmacy: YES/NO/DO NOT KNOW

   Comment: ……

3. Do your national regulations require a special licence for pharmacies to prepare medical products? YES/NO/DO NOT KNOW
   - o If YES: valid for all types of preparations and /or medicinal products? YES/NO/DO NOT KNOW
   - o OR restricted to stock preparations : YES/NO/DO NOT KNOW
   - o OR restricted to preparations delivered to other pharmacies? YES/NO/DO NOT KNOW
   - o OR limited to a maximal quantity? YES/NO/DO NOT KNOW
   - o Other restrictions?……..

   Comment: ……..

4. Which definitions are used in your country for pharmacy preparations?
   - o Magistral preparations:

   Please describe:……

Source (e.g. law, professional standard)……..

Please enclose document or web link:……..

o Officinal preparations:

Please describe:……

Source (e.g. law, professional standard)……

Please enclose document or web link:……

o ……

o Other types of preparations:

Please describe:……..

Source (e.g. law, professional standard)……

Please enclose document or web link:……

5. What types of pharmacies do you have in your country?

o Community pharmacies: YES/NO/DO NOT KNOW

o Hospital pharmacies: YES/NO/DO NOT KNOW

o Community pharmacies, which deliver medicinal products to other pharmacies.

o Hospital pharmacies which deliver medicinal products to other pharmacies

o Other: which

o ……..

Comments:……

II. General Safety and Quality Systems

6. Are special authorisations required for pharmacies (other than the 'normal' authorisation of a hospital pharmacy and/or community pharmacy) in your country for the preparation of medicinal products in pharmacies? YES/NO: DO NOT KNOW

o If yes, please describe:……

Note: GMP like, GMP for small quantities, other authorisation types.

7. Are there general safety - and quality standards in your country for

o Pharmacy preparations: YES/NO/DO NOT KNOW

- If yes, please describe requirements (enclose document or web link):
  ……..

8. Are pharmacy preparations subjected to the pharmacovigilance system for medicinal products? YES/NO/DO NOT KNOW
   - YES/NO/DO NOT KNOW
   - If yes, please describe requirements (enclose document or web link):
     ……..

9. Are there any additional safety and quality standards in your country for pharmacies for
   - Preparing larger batches: YES/NO/DO NOT KNOW
     1. if yes, please describe the definition for larger batch in your country;
        ……..
     2. Is preparation for stock building considered as large(r) batch? YES/NO/DO NOT KNOW
   - Delivery to other pharmacies? YES/NO/DO NOT KNOW
   - For any other operation linked to pharmacy preparations: YES/NO/DO NOT KNOW
   - If yes to any of these 3 questions, please describe source (enclose document or web link):……..
   - Other standards:

10. Do quality and safety standards for pharmacy preparations cover the following topics:
    - Quality system: YES/NO/DO NOT KNOW
    - Personnel: YES/NO/DO NOT KNOW
    - Equipment and premises: YES/NO/DO NOT KNOW
    - Documentation: YES/NO/DO NOT KNOW
    - Quality control (QC)
    - Recalls: YES/NO: DO NOT KNOW
    - Justification of therapeutic benefit/risk of the pharmacy preparation link): YES/NO/DO NOT KNOW
    - Quality of raw materials: YES/NO/DO NOT KNOW
    - Other standards:

    If yes, please describe:……

Please enclose document or web link:……..

11. Please answer the following questions concerning the use of raw materials (including packing materials) in pharmacy preparations:……
    - o Do pharmacies have access to raw materials with the required specifications?
    - o Is the performance of identity testing by the receiving pharmacy required? YES/NO DO NOT KNOW
    - o Is further analysis (e.g. content, purity) required? YES/NO/Do NOT KNOW

    If Yes, please describe which analyses:……..

III. Provisions and practices for preparation and delivery (supply) between pharmacies

12. Are medicinal products prepared in pharmacies required to have a marketing authorisation before they are delivered to a patient? YES/NO/DO NOT KNOW
    If yes, under which conditions:
    - o Batch size exceeding a certain quantity YES/NO/DO NOT KNOW
    - o If yes, which quantity:……
    - o Other:……

13. Is the preparation and delivery of pharmacy made medicinal products regulated in your national legislation
    - o Based on a specific (GMP type) contract between

    Pharmacies? YES/NO/DO NOT KNOW

    Pharmacies and companies that are not pharmacies? YES/NO/DO NOT KNOW

    Pharmacies and companies abroad? YES/NO/DO NOT KNOW

    - o Without contract between

    Pharmacies? YES/NO/DO NOT KNOW

    Pharmacies and companies that are not pharmacies? YES/NO/DO NOT KNOW

    Pharmacies and companies abroad? YES/NO/DO NOT KNOW

    - o Other: ……
    - o Please enclose relevant article of legislation or web link:……..

14. Is trade in pharmacy preparations between pharmacies regulated in your national legislation? YES/NO/ DO NOT KNOW

    If trade is permitted, please describe the conditions:

    - o License required? YES/NO/DO NOT KNOW
    - o Fulfilment of quality standards: YES/NO/DO NOT KNOW
    - o Written agreement between the pharmacies? YES: NO/DO NOT KNOW
    - o Absence of an equivalent medicinal product with marketing authorisation on the market
    - o Availability upon request of authorities of chemical-pharmaceutical data:
        - Microbiological data for sterile/aseptic preparations: YES/NO/DO NOT KNOW
        - Environmental monitoring? YES/NO/DO NOT KNOW
    - o Other :……..
    - o Are pharmacies permitted to export their pharmacy preparations? YES/NO/DO NOT KNOW

    Please enclose all documents or web link (legislation, ordinance, letter, professional standards) relevant for this question (legislation, ordinance, circular letter, professional standards):……..……..

15. Do you have pharmacies in your country, which trade own pharmacy preparations to other pharmacies? YES/NO/DO NOT KNOW

    If yes, do you think that the number of pharmacies which trade own pharmacy preparations to other pharmacies in your country **over the last 10 years** has INCREASED/DECREASED? DO NOT KNOW.

    In your view, what are the main reasons or the change in the number of pharmacies, which trade own preparations to other pharmacies in your country over the last 10 years?

    - o Level of education of personnel: YES/NO/DO NOT KNOW
    - o Equipment and premises? YES/NO/DO NOT KNOW
    - o Compliance of community pharmacies with national quality and safety standards: YES/NO/DO NOT KNOW
    - o Compliance of hospital pharmacies with national quality and safety standards: YES/NO/DO NOT KNOW

- o New regulations (restriction/authorisation of these activities): YES/NO/ DO NOT KNOW
- o Other::……..

What is your expectation for the number of pharmacies, which trade own pharmacy preparations to other pharmacies **in the next 10 years to come**? Increased/decreased/ do not know
Comment: ……..

16. What is your estimation of the number of pharmacy preparations with a marketing authorisation issued by your national Drug regulatory authority?
    - o 0-10: YES/NO/DO NOT KNOW
    - o 10-15: YES/NO/DO NOT KNOW
    - o 50-100: YES/NO/DO NOT KNOW
    - o > 100: YES/NO/DO NOT KNOW

IV Quality and safety of pharmacy preparations

17. Do you have data from national control authorities, academic institutions (objective, independent) on the quality and safety of the pharmacy preparations?

    YES/NO/DO NOT KNOW

    Comments:……..

    If yes, do these data point out to specific risks concerning pharmacy preparations?
    - o Quality system: YES/NO/DO NOT KNOW
    - o Personnel? YES/NO/DO NOT KNOW
    - o Equipment and premises: YES/NO/DO NOT KNOW
    - o Documentation: YES/NO/DO NOT KNOW
    - o Quality control: YES/NO/ DO NOT KNOW
    - o Recalls: YES/NO/DO NOT KNOW
    - o Safety: YES/NO/DO NOT KNOW
    - o Other: ……

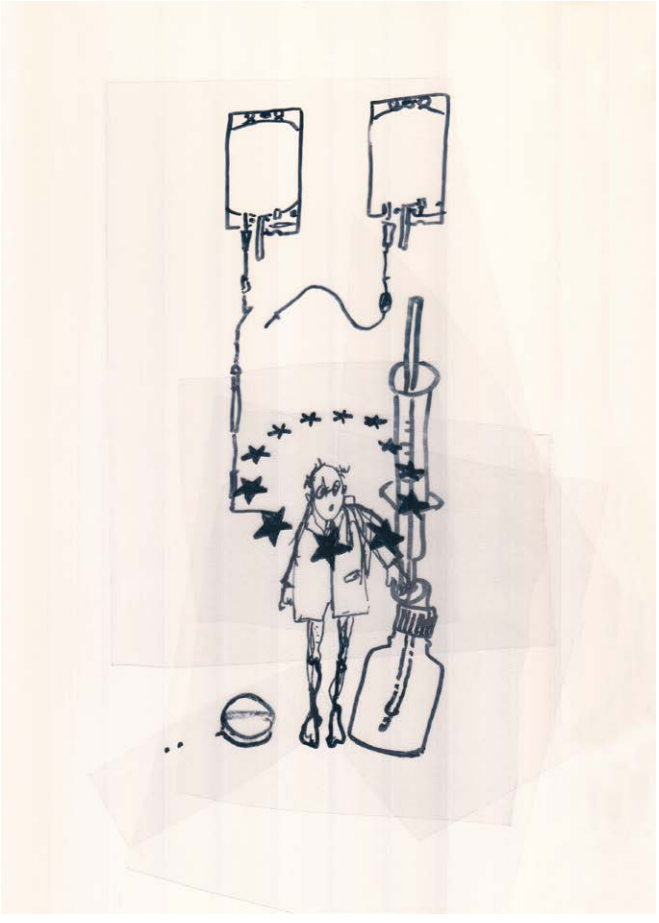
    Comments:……..

18. Do you think that your national authorities could support harmonisation of the quality and safety standards for pharmacy preparations between the states

parties of the Convention on the Elaboration of a European Pharmacopoeia? YES/NO/DO NOT KNOW.

Comment:……..……

- Pharmacy preparations: YES/NO/DO NOT KNOW
- If yes, please describe requirements (enclose document or web link): ……..
- Preparation of medicines in other healthcare establishments? YES/NO/DO NOT KNOW
- If yes, please describe requirements (enclose document or web link): ……..



Chapter 3

Impact of the Council of Europe Resolution on quality and safety assurance requirements for medicinal products prepared in pharmacies for the special needs of patients

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Abstract

Introduction and objective

The regulation of pharmacy preparations, especially for standards for quality assurance and safety, is not harmonised across Europe and falls under the national competencies of individual states. There are concerns about quality control and safety for the medicinal products made in pharmacies which is widespread in European countries. There are, however, good reasons to continue this practice which is able to tailor preparations to the specific needs of a particular patient or patient group and to provide a supplementary source of supply when an industrially manufactured product, which is authorised for marketing is not available or when there are temporary shortages of licensed medicines.

In seeking to provide guidelines for legislation and acting on the advice of an expert group dealing in Pharmaceutical practices, the Committee of Ministers of the Council of Europe passed a resolution in 2011. The Council of Europe Resolution provides authorities and pharmacists with the means to reinforce safety measures for medicinal products prepared in pharmacies and to harmonise quality assurance and safety standards. It dealt with aspects of pharmacy preparation such as quality standards for preparation and distribution, marketing authorisation, product dossiers, labelling, reporting, and safety.

In 2013 and 2014 the Committee of Experts carried out a survey to evaluate the impact of the Resolution within a cross section of member states. The objectives of this study were both to monitor the extent to which the recommendations had been enshrined in national legislation and also to understand current differences in legislation and practice between the member states.

Methods

In the resolution of 2011 the member states were recommended to adapt their legislation in line with its provisions. The survey that was carried out in 2013 and 2014 followed the recommendations in the resolution. A questionnaire was made and sent to a cross section of member states.

Results

Among the member states involved, the results of this survey show a clear commitment to implement the recommendations of the resolution.

Conclusions

This report presents the results of the survey with a discussion of outstanding issues.

1. Introduction

In European countries, medicines prepared in pharmacies continue to provide an important resource for patients, especially if a medicinal product manufactured on an industrial scale and authorised for marketing is not available on the market or is in short supply. However, the regulation of pharmacy preparations, notably on standards for quality assurance and safety, is not harmonised throughout Europe and falls under the national competencies of individual states. This situation has, for a number of years, received the attention of the Committee of Experts on Quality and Safety Standards for Pharmaceutical Practices and Pharmaceutical Care (CD-P-PH/PC), coordinated by the Council of Europe's European Directorate for the Quality of Medicines and HealthCare (EDQM).

In 2008-2009 a survey carried out among the State Parties to the Convention on the Elaboration of a European Pharmacopoeia concluded that there were significant differences in the regulation of pharmacy-made medicinal products, as well as a gap in quality assurance between preparations in pharmacies and medicines prepared by the pharmaceutical industry [1]. At a workshop in 2009, the CD-P-PH/PC discussed the survey results with experts from health authorities and with practitioners working in this field. This enabled them to identify key elements of standards for pharmacy preparations in Europe [2].

In 2010, the Committee of Experts made proposals for harmonising quality and safety standards for pharmacy preparation of medicinal products in Europe, which led, in 2011, to the adoption by the Committee of Ministers, of Resolution CM/Res AP(2011)1 (hereafter: the Resolution) [3]. This provided authorities and pharmacists with the means to reinforce quality and safety measures for medicinal products prepared in pharmacies, and member states were recommended to adapt their legislation in line with its provisions.

In 2013 and 2014 the Committee of Experts carried out a survey to evaluate the impact of the Resolution within a cross section of member states. The objectives of this study were both to monitor the extent to which the recommendations had been enshrined in national legislation and also to understand current differences in legislation and practice between the member states. The results are described in this article.

It is important to consider that the EU regulation of medicinal products has two pillars: the marketing authorisation of the medicinal product, and the authorisation for manufacturing and wholesale.

These legal aspects are addressed and explained in a separate article [4].

2. Methods

A survey questionnaire was prepared by a working party of the CD-P-PH/PC coordinated by the corresponding author. This was sent to experts from the States Parties of the Convention on the Elaboration of a European Pharmacopoeia and the delegations of the European Committee on Pharmaceuticals and Pharmaceutical Care (CD-P-PH).

Each of the questions in the survey questionnaire makes reference to an article in the Resolution text. A selection of the most relevant parts of the Resolution was included in the questionnaire. Per question it was asked which changes had occurred since the adoption of the resolution text on 19 January 2011. The data of the following 12 countries were included in the survey results: Belgium (BE), the Czech Republic (CZ), Denmark (DK), Finland (F), Ireland (IE), Italy (IT), the Netherlands (NL), Poland (PL), Portugal (PT), Serbia (RS), Switzerland (CH) and the United Kingdom (UK).

Details of the survey questionnaire are included in an annex that is attached to this article.

The objective of the survey was twofold:

- to audit the effects of the Resolution with respect to measures taken by the member states to adapt their legislation in line with its recommendations;
- to assess differences between the member states in terms of their regulations covering pharmacy preparations.

In addition to the questionnaire, a number of teleconferences were held between parties concerned, in order to clarify relevant approaches adopted by the member states.

3. Results

The results relating to practice and legislation in 12 member states were collected and are presented in the summary table below. The summary table indicates whether the countries comply with the different recommendations of the Resolution. In this context it is important to keep in mind that a Resolution of the Council of Europe is not binding legally and is less stringent than, for example, a European Directive such as Directive 2001/83/EC or a European Regulation such as Regulation (EC) No 726/2004. The most relevant comments made by the countries are presented in this results section.

Summary table

Resolution pharmacy preparation	1 BE	2 DK	3 FI	4 UK	5 NL	6 PL	7 CZ	8 IE	9 IT	10 PT	11 RS	12 CH	total
pharmaceutical equivalents (3.1)	0	1	0	1	1	0	0	1	0	0	0	1	5
preparing and dispensing pharmacy (regulations or contractual agreement; 3.2)	1	1	1	1	1	1	1	1	1	0	1	1	11
Preparation authorisation or preparation licence for pharmacies (10.1)	1	1	1	1	1	1	1	1	1	0	1	1	11
company licence for pharmacy preparations (10.2)	1	1	1	1	1	1	1	1	1	1	1	1	12
preparation process (4) (GMP for high risk preparations)	1	1	1	1	1	1	0	1	1	0	1	1	10
product dossier (5) (required for stock preparations)	1	1	1	1	1	1	1	0	0	0	1	0	8
marketing authorisation (6) (MA for pharmacy preparation)	0	0	0	0	0	0	0	0	0	0	0	1	1
labelling (7) with mentioned elements	1	1	1	1	1	1	1	1	1	1	1	1	12
pharmacopoeia compliance (8)	1	1	1	1	1	1	1	1	1	1	1	1	12
transparency and safety (11)													
reporting of quality and safety (11.1)	1	1	1	1	1	0	0	1	0	1	1	1	9
notification or announcement (11.2)	0	1	1	1	1	0	0	0	1	0	0	1	6
inventory pharmacy preparations (11.3)	0	1	1	0	0	0	0	0	0	0	1	0	3
surveillance (11.5)	0	1	1	1	1	0	0	1	1	0	0	1	7
distribution (13)													
GDP compliance	1	1	1	1	1	1	1	1	0	0	1	0	9
export and import of pharmacy preparations	1	1	1	1	1	1	1	1	1	1	1	1	12

1 = complies with resolution
0 = does not comply with resolution

The results are discussed below in an order which corresponds to the main items of the Resolution [3].

The value of pharmacy preparations and the responsibility of health care professionals (item 3)

The Resolution stipulates that pharmacy preparations are not advisable if a suitable pharmaceutical equivalent, with a marketing authorisation, is available. In 5 out of the 12 countries that responded, preparations are not normally made in the pharmacy if a suitable authorised medicinal product is available on the market.

In 6 out of 12 countries pharmacy preparations can be made if a suitable pharmaceutical equivalent is on the market. One of these six countries responds that it is legally not forbidden to make a pharmacy preparation even if a licensed equivalent is on the market. Two other countries are considering a change in legislation. Three countries respond that pharmacists are able to propose the equivalent if it is on market instead of preparing the pharmaceutical preparation.

An additional reaction of one of the countries was that there is often pressure from the pharmaceutical manufacturers who check whether pharmacists are making products identical, or nearly identical, to their medicinal product with marketing authorisation. Another country commented that recent cases have occurred where a pharmacy had to stop preparation upon the request of the authorities, or because of a court decision related to a complaint by a manufacturer or private company.

For preparing and distributing pharmacies (PDPs), who prepare medicinal products in their pharmacy and distribute these products to a dispensing pharmacy, the national requirements seem to be more stringent. In the Netherlands it is not allowed for these PDPs to prepare and distribute a medicinal product if a licensed pharmacotherapeutic alternative is available on the market [5]. In the UK, the producer of a pharmacy preparation should have systems in place to ensure that medicines are not supplied where a licensed alternative exists. Documentary evidence of the special need of the patient should be made available on request of the competent authority in the UK [6].

Preparation process (Item 4)

The Resolution recommends that the Good Manufacturing Practice (GMP) quality system should be used for “high-risk preparations” and that the Good preparation practices (PIC/S GPP) Guide be used for “low-risk preparations” [3].

A possible model procedure for risk assessment, described in item 5.2, and in note 1 of the Resolution, provides an aid for helping to distinguish between two risk levels for preparations (“high-risk” and “low-risk”). The application of other best-

practice standards with an equivalent level of quality is according to the Resolution possible, depending on the national legislation or guidance.

In 10 out of 12 member states responding, GMP is the required quality system for "high-risk preparations" and in some it is required for all preparations.

In the Czech Republic, a quality system comparable to the PIC/S GPP Guide applies in cases of high-risk preparations. In Italy, a higher quality standard that approximates to GMP is required for sterile production. In Switzerland a risk assessment, which is mandatory for every product, defines the minimum conditions of the quality system. The risk assessment also determines the competent authority (national or cantonal), which provides the authorisation for production.

Product dossier (Item 5)

The Resolution requires that product dossiers, containing essential information about the product, should be available for stock preparations. As described in note 2 of this Resolution, the product dossier contains information about: the justification for, and the preparation process of, the pharmacy preparation; the composition; the in-process controls and quality controls of the finished product; the results from test batches; the validation of the preparation process and its analytical methods; the stability considerations; and information for the patient about its use. Relevant information should be shared with the patient and/or carer, although a patient leaflet is not required for pharmacy preparations.

For extemporaneous preparations, it will usually not be possible to compile a complete product dossier as it could lead to a delay in the supply of necessary medicines.

Eight of the 12 countries comply with these recommendations of the Resolution. Although a product dossier is not specifically mentioned in the Belgian and UK regulations, the requirements in these countries are comparable to those given in the Resolution. In Poland, there are only extemporaneous preparations.

In 4 of the 12 countries there is not yet a requirement for having a product dossier. Two countries have indicated that the implementation of a product dossier is under consideration.

Marketing authorisation (Item 6)

The Resolution requires that the competent drug regulatory authorities should consider establishing, the requirement to obtain a marketing authorisation, including full compliance with GMP, where the preparation is carried out on a scale comparable to the industrial level, distribution takes place, and if an authorised medicinal product or a pharmaceutical equivalent is on the market.

In only 1 out of the 12 member states the requirement for a marketing authorisation for pharmacy preparations is partially implemented.

In Denmark some hospital pharmacies manufacture products that obtained a marketing authorisation in the 1980s when authorisation was achieved without extensive documentation of safety and efficacy. If hospital pharmacies now wish to obtain a marketing authorisation for a medicinal product, the requirements would be the same as for all other medicinal products. No such application has yet been seen.

In the Netherlands, the procedures for applications for a marketing authorisation are mostly used by the pharmaceutical industry although there are some medicinal products made in pharmacies, which have obtained a marketing authorisation.

In Switzerland, a marketing authorisation for a pharmacy preparation can be obtained through a simplified approval procedure that is defined in their regulations.

Labelling (Item 7)

The Resolution states that correct labelling, with a range of prescribed details, is essential for patient safety. For example, the name and address of the preparing pharmacy and the name and address of the dispensing pharmacy should be on the label. Moreover, some details concerning the pharmacy preparation itself are required such as the composition, the expiry date, special storage conditions, directions for use and the route of administration.

All 12 of the member states reported that the recommendations of the Resolution, with regard to labelling, are included in their legal requirements.

Compliance with the pharmacopoeial requirements (Item 8)

In the Resolution, compliance with pharmacopoeial requirements is obligatory. Active pharmaceutical ingredients and excipients used for the pharmacy preparations, dosage forms and containers must comply with the relevant chapters and monographs of the European Pharmacopoeia or, in the absence thereof, of a national pharmacopoeia.

Where no applicable pharmacopoeial general chapters or individual monographs exist, then the chemical, pharmaceutical and microbiological quality of the starting materials should be suitable for pharmaceutical use as demonstrated with validated methods.

In all 12 member states, compliance with pharmacopoeial requirements is obligatory.

Authorisation for pharmacies, or licences for private companies, making preparations for pharmacies (Item 10)

Authorisation for pharmacies (item 10.1)

In general, authorisation by the competent authorities or bodies is a prerequisite for a pharmacy to carry out operations. The Resolution recommends that, if considered appropriate to guarantee the quality and safety of pharmacy preparations, the authorities should provide for an additional authorisation or a licence for preparation. An additional authorisation or licence can be granted or suspended, depending on compliance with its conditions.

Eleven out of 12 respondent countries comply with this recommendation. In Portugal the recommendation is under consideration. In Belgium, Finland, Denmark and the UK [6], there are legal provisions that allow under strict conditions that a preparing pharmacy makes a pharmacy preparation for a dispensing pharmacy.

Licence for companies (item 10.2)

The Resolution states that in some countries, the preparation of medicinal products is performed at the request of pharmacies by companies that are not pharmacies. In this case, a licence for manufacture (for EU member States, a manufacturing licence and full compliance with GMP) issued by the competent authority should be mandatory.

Seven out of the 12 respondent countries report that a licence exists for companies to make preparations for pharmacies. The remaining five countries, Denmark, Finland, Poland, the Netherlands and Italy, also comply with the Resolution because they report that these companies do not exist or that it is legally not permitted for companies to make preparations for pharmacies.

Regulation or contractual agreement (item 3.2)

If the preparing pharmacy and the dispensing pharmacy are not identical, their different responsibilities, including the sharing of those elements of the product dossier essential for the safe use of the product by the patient, should be defined either in regulations or a contractual agreement [3]. Pharmacy preparations should always be distributed to a dispensing pharmacy because this pharmacy receives the prescription and provides the pharmacy preparation to the patient. The preparing pharmacy should be responsible for ensuring that an appropriate quality assurance system is in place.

Eight out of the 12 respondent countries report that an agreement between the preparing and dispensing pharmacy exists. In Belgium the law requires that there is a contractual agreement between the preparing pharmacy and the dispensing pharmacy, which lists all products that are distributed to the dispensing pharmacy.

In Denmark, a contract between the preparing pharmacy and the dispensing pharmacy is not required since it is covered by the national legislation.

Three out of the 12 respondent countries report that the preparing pharmacy and the dispensing pharmacy have to be identical, which is allowed for in the Resolution.

One country did not respond because changes in national regulation are foreseen.

In the EU, medicinal products are regulated by Directive 2001/83/EC and Regulation (EC) No 726/2004 (hereafter: EU legislation). This EU legislation offers opportunities for pharmacy preparations, but only under certain strict conditions as defined in these regulations. Pharmacies specialised in preparation do not (always) fulfill these strict conditions. The legal aspects are addressed and explained in a separate article [4].

Transparency and safety (Item 11)

The Resolution lists several points under this overall heading:

- Reporting of quality and safety issues (item 11.1).

The Resolution recommends that all quality and safety issues arising from the use or making of pharmacy preparations should be recorded and notified to the competent national authorities. An appropriate system for reporting quality and safety issues should be put in place, which allows for a link between this notification, the product, the preparing and dispensing pharmacies, and the preparation process.

Nine out of 12 member states have a system in place for reporting quality and safety issues. In the remaining countries such a system is missing or needs improvement.

- The system of notification or announcement (item 11.2)

The Resolution states that, with a view to dealing with high-risk preparations, the competent national authorities should obtain relevant information on the preparation activities performed in each pharmacy. The establishment of an appropriate notification system should be considered.

In six out of 12 countries responding, there is a notification system for preparation activities. In the remaining countries the pharmacies do not need to inform the authorities about their preparation activities. In Ireland, a notification system does not exist for pharmacies, but for holders of a specials licence it is specified which type of products they are allowed to make and in case of changes they have to inform the authorities.

- Inventory for pharmacy preparations

The Resolution encourages the establishment of national inventories, with a view to transparency as regards pharmacy preparations for stock. The national inventory should cover the following topics:

a. names of the preparing pharmacies;

b. full composition of the available pharmacy preparations;

c. preparing pharmacies' portfolio of different preparations.

Three of the 12 responding countries reports that they have implemented an inventory or an alternative. In Denmark and Finland, the required information is available for the authorities through the notification system.

- Surveillance

The competent authorities should perform risk-based inspections, for example, by using the information obtained through the notification system. Competent authorities should have powers to suspend preparation activities, in, for example, the case of deficiencies in the quality of the product or if the pharmacy does not comply with the regulations.

Seven out of the 12 countries responding perform risk-based inspections in pharmacies.

Distribution of pharmacy preparations (Item 13)

The Resolution contains two separate points under this heading:

- Compliance with good distribution practices (GDP)

The Resolution states that pharmacies or companies preparing medicinal products under their responsibility upon the request of pharmacies should comply with good distribution practices (GDPs).

This is currently the case in nine out of the 12 respondent countries. Belgium, the Czech Republic and Ireland report that GDP is required for companies, but not for pharmacies.

- The export or import of pharmacy preparations.

Other than to meet an individual patient's needs, export/import of pharmacy preparations from a member state to another member state should not take place, unless bilateral agreements exist. As long as no uniform and mutually agreed quality requirements for medicinal products without marketing authorisation are available, and as long as the inspectorates' competencies are not regulated, export should not take place [3].

All countries comply with these recommendations. In nine out of 12 countries no export or import occurs. In Denmark, the United Kingdom, Ireland and Switzerland some export or import occurs, but this is mainly to cover individual patient's needs, which is allowed for in the Resolution.

4. Discussion

The results of this survey show that, in general, the Resolution's recommendation that suitable authorised medicinal products have priority, and that pharmacy preparations are only to be made in special cases when there is a medical need, is followed. However, in this matter a distinction should be made between pharmacies that dispense the medicinal products they have made to their own patients and pharmacies that distribute the products they have made to other pharmacies, respectively.

In EU legislation it is not forbidden to make a pharmacy preparation if a licensed pharmaceutical equivalent is available on the market, but this is restricted to preparing pharmacies that dispense the medicinal products they have made to their own patients. However, although it is not explicitly forbidden in EU legislation, it is in general not considered appropriate practice to make a medicinal product in a pharmacy if a pharmaceutical equivalent is available on the market.

The survey shows that in some countries, like the UK and the Netherlands, it is not permitted for pharmacies that distribute their products to other pharmacies, to make medicinal products for which there is a pharmaceutical equivalent with a marketing authorisation available on the market.
The Resolution recommends that for the preparation process an appropriate quality assurance system should be put in place. The results of this survey support the recommendation of the Resolution that GMP is the required quality system for "high-risk preparations". In most of the respondent countries GMP is a requirement for high-risk preparations, but there are also countries where a quality system comparable to the PIC/S GPP Guide applies in cases of high-risk preparations.

It is encouraging that the recommendation of the Resolution concerning product dossiers for stock preparations, which is relatively new, is followed in European countries. There are countries where this concept of product dossiers is already existing or planned for implementation, but there are also countries where implementation is not yet envisaged. We would like to emphasise the importance of a product dossier describing each specific product's quality properties as well as the site-specific preparation conditions. A product made under the GMP requirement, but with a product dossier of insufficient quality, is in our opinion not in the interest of the patient.

This survey shows that the recommendation of the Resolution that the competent drug regulatory authorities should consider establishing, the requirement to obtain a marketing authorisation, including full compliance with GMP, for specific pharmacy preparations and in specific cases is hardly implemented. It would be in the interest of the patient to work further on the implementation of this recommendation.

Concerning the topic of authorisation for pharmacies, or licenses for private companies making preparations for pharmacies, this survey shows that there is a wide diversity between countries.

The EU legislation on medicinal products – Directive 2001/83/EC and Regulation No (EC) 726/2004 – provides a number of exceptions through which the EU legislation or specific provisions, for example, the requirement for a marketing authorisation, do not apply. Given the recent case law of the European Court of Justice, it can be argued that from a legal point of view there is no or very little room for pharmacies specialised in preparation distributing their products to other pharmacies [4]. We believe that well-equipped pharmacies specialised in pharmacy preparation can provide a higher level of quality assurance and safety and are in the interest of patients under the strict condition that they fulfil relevant requirements as the ones mentioned in the Resolution. Moreover, these pharmacies may be of help to resolve shortages of medicinal products, temporary or otherwise, which occur relatively frequently nowadays.

Concerning the transparency and safety of pharmacy preparations, the survey shows that many countries comply with the recommendations of the Resolution, but there is still room for improvement in particular concerning the notification system and the national inventories. In our opinion, it is of crucial importance for the national authorities to have an overview of the preparation activities performed in each pharmacy in order to carry out a risk-based inspection programme which includes all factors that affect the efficacy, tolerability and safety of the medicinal product for the patient.

The survey shows that companies preparing medicinal products under their responsibility upon the request of pharmacies comply in general with good distribution practices (GDP), but for pharmacies that prepare and distribute medicinal products to other pharmacies this is not the case in some countries. From the perspective of the patient, compliance with good distribution practices (GDP) should be obligatory in our view, irrespective of where the product is made.

Regulation of pharmacy preparations is currently not harmonised throughout Europe. Implementation of standards established by the Council of Europe for quality assurance and safety of medicines prepared by compounding pharmacies can help to prevent serious incidents of the type that have occurred in areas outside of Europe, notably in the US [7-9].

5. Conclusion

Norms established by the Council of Europe for quality assurance and safety of medicines prepared by pharmacies specialised in preparation have been enshrined in Resolution CM/ResAP(2011)1. The Resolution is a major breakthrough in pro-

tecting patient safety and in preventing gaps in the quality and safety between medicinal products prepared in pharmacies and those made in industrial settings. Here, we have investigated the progress in implementation of the Resolution into national legislation.

National authorities must make use of all available information when adapting their legislation, and the Resolution on pharmacy preparations is one of the factors for the authorities to take account of. Adapting legislation is a long-term process and the period between the acceptance of the Resolution in 2011 and the carrying out of this survey may be too short to assess the eventual impact. With this reservation, the overall results of the survey indicate that among the countries involved there is, in general, a clear commitment to implement the recommendations of the Resolution.

Key messages

What is already known on this subject

1. It is common practice throughout member states to allow pharmacy preparations for the special needs of patients for which no licensed medicinal product is available on the market.

2. With a view to ensuring appropriate patient safety in Europe, the Council of Europe Resolution CM/ResAP(2011)1 lays down the requirements for the quality and safety assurance of medicinal products prepared in pharmacies for human use. It also provides an aid for helping to distinguish between two risk levels for preparations ("high-risk" and "low-risk").

What this study adds

1. The article provides insights into the progress of the implementation of Resolution CM/ResAP(2011)1 within a cross section of member states of the Council of Europe.

2. The article also highlights the role of Resolution CM/ResAP(2011)1 in preventing gaps in the quality and safety between medicinal products prepared in pharmacies and those made in industrial settings and in protecting patient safety in health care establishments. Pharmacies specialised in pharmacy preparation can provide a higher level of quality assurance and safety and are in the interests of patients if they fulfil relevant requirements as the ones mentioned in the Resolution.

3. The Resolution is available to authorities and pharmacists in order to prevent serious incidents with medicinal products prepared in pharmacies.

Acknowledgements

The authors would like to thank the delegates of Council of Europe's Member States.

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Annex 1

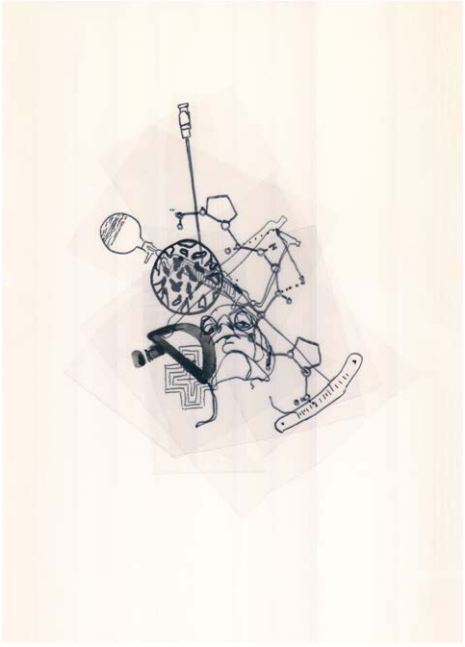
Sender
Country:
Subject

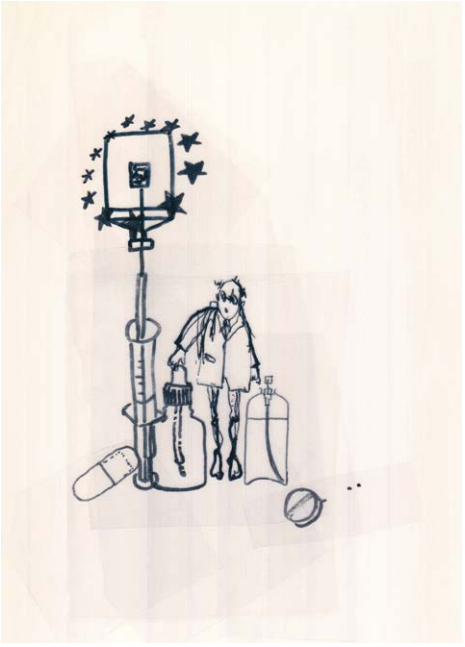
Implementation of the Resolution on quality and safety assurance requirements for medicinal products prepared in pharmacies for the special needs of patients.

Questionnaire
Some clarifying remarks concerning the regulation for pharmacy preparations in your country:

Resolution text	question	Comments
3.1. (pharmaceutical equivalents on the national market) and	- is it implemented in legislation that a pharmacy preparation is not advisable if a pharmaceutical equivalent is available on the national market?	
3.2. (added value and responsibility of health care professionals)	- are the responsibilities of the preparing pharmacy and the dispensing pharmacy (if these pharmacies are not identical) defined in: a/ regulations? b/ a contractual agreement?	
4. (preparation process)	- is GMP applicable for high risk preparations?	
5. (product dossier)	- are product dossiers, as described in note 2, required for stock preparations?	
6. (marketing authorisation)	- has the regulatory authority considered establishing the requirement for obtaining a marketing authorisation for pharmacy preparations?	
7. (labelling)	- is this implemented in your country?	
8. (compliance with pharmacopoeial requirements)	- is this implemented in your country?	
10.1 (authorisation of pharmacies)	- is there an additional authorisation or licence for preparation?	
10.2 (licence for companies)	- in case you have such companies: is a licence for manufacture mandatory for these companies?	
11 (transparency and safety)		
11.1 (reporting of quality and safety issues)	- is there an adequate system for reporting quality and safety issues? (please attach)	
11.2. (notification or announcement system)	- do you have a notification system concerning the preparation activities performed in each pharmacy? (please attach details)	
11.5 (surveillance)	- does the competent authority performs risk-based inspections? (11.5) (please provide details how this is performed)	
11.3 (inventory for pharmacy preparations)	- do you have a national inventory for pharmacy preparations?	

Resolution text	question	Comments
13. (Distribution of pharmacy preparations?)	- do pharmacies or companies, preparing medicinal products upon the request of pharmacies, have to comply with good distribution practices (GDP) in your country (13.1)? - does export or import of pharmacy preparations take place in your country (13.2)?	





Chapter 4

Legislation on the preparation of medicinal products in European pharmacies and the Council of Europe Resolution

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ABSTRACT

Introduction

The rights of patients should be sufficiently protected even when an appropriate authorised medicine does not exist or is unavailable on the market. The Resolution, which was adopted by the Committee of Ministers of the Council of Europe in 2011, aims at harmonising quality and safety standards for pharmacy preparation of medicinal products in Europe.

Two pillars of EU regulation and the exceptions to them

The system of regulation of medicinal products is built upon two pillars: the marketing authorisation of the medicinal product and the licence for manufacturing and wholesale. This article provides insight into the recent interpretation of the European Court of Justice (ECJ) concerning the scope of European Union (EU) regulation of medicinal products and the circumstances in which the EU regulation does not apply: pharmacy preparations, specialities and the compassionate use of medicines, including manufacturing licence.

EU regulation and the Resolution concerning pharmacy preparation

Pharmacy preparations are allowed under certain strict conditions according to EU regulations. However, pharmacies specialised in preparation and distributing medicinal products to local pharmacies do not fulfil these strict conditions in EU regulation. Apart from the legal context, relevant standards for safety and quality assurance are needed in Europe in order to protect patients' rights and to avoid risks from pharmacy preparations.

Discussion and conclusions

The Council of Europe Resolution provides a means of establishing standards for safety and quality assurance for pharmacy preparations through Good Manufacturing Practice (GMP) Guidelines. The Resolution is available to authorities and pharmacists in order to prevent incidents with medicines prepared in pharmacies which may threaten patients' safety. The authors conclude that pharmacy practices have changed over time in Europe and this may imply a reason for a reform of EU regulation on medicinal products.

1. Introduction

The preparation of medicines in pharmacies is important in order to accommodate individual patients' needs in Europe. This is, in particular, the case if an appropriate authorised medicine does not exist or is unavailable on the market. European Union (EU) regulation determines under which conditions a marketing authorisation is required in order to place a medicinal product on the market and under which conditions a manufacturing and wholesale licence is required. However, it allows some exemptions such as for pharmacy preparations. Some aspects of pharmacy preparations, notably the standards for quality assurance and safety, are not harmonised throughout Europe and therefore fall under the competencies of individual member states.

The Committee of Experts on Quality and Safety Standards in Pharmaceutical Practices and Pharmaceutical Care (CD-P-PH/PC), hereafter, the Committee of Experts, carried out a survey in 2008-2009 among the state parties to the *Convention on the Elaboration of a European Pharmacopoeia*. This was coordinated by the European Directorate for the Quality of Medicines & HealthCare (EDQM) of the Council of Europe. The survey results showed a wide variety between the respondent countries in the quality assurance and standards for medicinal products made in pharmacies. In addition, it demonstrated a gap in standards for quality assurance between medicines prepared in pharmacies and those prepared by the pharmaceutical industry.[1] The results were discussed among experts from the health authorities and from the field at a workshop in 2009. They aimed to identify criteria and key elements of standards for pharmacy preparation in Europe.[2] Subsequently, the Committee of Experts proposed a draft resolution for harmonising quality and safety standards for pharmacy preparation of medicinal products in Europe. This led to the adoption of Resolution CM/Res AP(2011)1[3] (hereafter: the Resolution) by the Committee of Ministers of the Council of Europe in 2011 and the Committee recommended that member states should amend their legislation in line with the provisions of the Resolution.[3] The Resolution was put at the disposal of the authorities and pharmacists in order to prevent incidents with medicines prepared in pharmacies which may threaten patients' safety. The Committee of Experts has evaluated the effect of the resolution in 2013-2014.[4]

Here, we outline the pillars of EU regulation of medicinal products including the circumstances in which the EU regulation does not apply. It provides insight into the recent interpretation of the European Court of Justice (ECJ) concerning the scope of EU regulation of medicinal products and the exceptions to it. Moreover, the article emphasises that relevant standards for safety and quality assurance, such as the ones provided in the Resolution, are needed in Europe in order to protect patient rights and to avoid risks to patients associated with pharmacy preparations. Finally, we assess whether change to pharmacy practice over time, as well

as recent case law, provide reason for the reform of EU regulation on medicinal products.

2. The two pillars of EU regulation and the exceptions to them

2.1 The two pillars of regulation

The system of regulation of medicinal products is built upon two pillars: the marketing authorisation of the medicinal product and the licence for manufacturing and wholesale.

In the EU, medicinal products are regulated by Directive 2001/83/EC[5] and Regulation (EC) No 726/2004.[6] The Directive establishes in article 6 (1) that no medicinal product may be placed on the market of a member state unless a marketing authorisation has been issued by the competent authorities of that member state or of the European Commission (EC). Regulation (EC) No 726/2004 lays down the procedure for obtaining a marketing authorisation for certain types of medicinal products (article 3 Regulation (EC) No 726/2004). Every marketing authorisation issued through this procedure is valid throughout the entire EU. In addition, Directive 2001/83/EC states the marketing authorisation procedures for medicinal products that are not addressed in Regulation (EC) No 726/2004. Those products may obtain national approval in one or more member states.[7]

The Directive also establishes that manufacturing of the medicinal products is subject to the holding of a licence issued by the member states (article 40 (1) Directive 2001/83/EC). Moreover, the Directive also states that the wholesale distribution and storage are covered by an authorisation granted by the member state in accordance with this Directive (article 77 (1) Directive 2001/83/EC).

The two pillars only apply in cases where the Directive 2001/83/EC itself is applicable. The Directive applies to any medicinal product that is prepared industrially or manufactured by a method involving an industrial process as determined by article 2 (1) of Directive 2001/83/EC. Products that do not fulfil the conditions of article 2 are not subject to the provisions of the Directive. The meaning of article 2 will be explained in more detail below on the basis of case law of the ECJ: *Abcur AB versus Apoteket.*

2.2 Exceptions to the two pillars of Directive 2001/83/EC

The current Directive 2001/83/EC contains a number of exceptions as regards the above-mentioned pillars. The most important exceptions, as far as they are relevant in relation to the Resolution are: pharmacy preparations, specialties, compas-

sionate use programme and manufacturing licence exception. These are all referred to as exceptions although their scope and legal nature differs.

2.2.1 Pharmacy preparations

Article 3 of Directive 2001/83/EC states, among other things that the Directive shall not apply to:

> *Magistral Formula, that is any medicinal product prepared in a pharmacy in accordance with a prescription for an individual patient; and to,*
>
> *Officinal Formula that is any medicinal product which is prepared in a pharmacy in accordance with the prescriptions of a pharmacopoeia and is intended to be supplied directly to the patients served by the pharmacy in question.*

Both definitions contain multiple cumulative requirements. The exceptions only apply if all of the requirements are fulfilled. In that case, neither the marketing authorisation nor the manufacturing and wholesale licences, as established in the Directive, are required. The exception for these requirements is also applicable in the case of the preparation of a medicinal product for which an alternative medicinal product with a marketing authorisation is available on the market. A recent judgement of the ECJ elucidated the requirements.

Abcur AB versus Apoteket

In the case *Abcur AB versus Apoteket,*[8] Apoteket, a Swedish state-owned company which had the exclusive right to sell medicines to the public until July 2009, produced and sold two medicines (Noradrenalin APL and Metadon APL) without having marketing authorisations for those products. Abcur produced and sold two comparable medicines (Noradrenalin Abcur and Metadon Abcur) for which the company had obtained marketing authorisations. Abcur had put in a claim for compensation for economic loss against Apoteket, because of the promotion of unauthorised medicinal products by Apoteket. The Swedish court suspended the case in order to request a ruling from the ECJ on the meaning of specific provisions of Directive 2001/83/EC.

The ECJ first clarified the scope of Directive 2001/83/EC as determined in article 2. The Directive applies to medicinal products for human use intended to be placed on the market in member states and either prepared industrially or manufactured by a method involving an industrial process. According to the ECJ, a medicinal product manufactured by a method involving an industrial process is characterised through a sequence of operations. These can be either mechanical or chemical, and are intended for the production of large amounts of a standardised product. This implies that Directive 2001/83/EC may apply in the case of standardised production of large amounts of a medicinal product intended for storage or wholesale

activities, and in the case of production on a large scale or in series of *magistral formulae* in batches.

The ECJ ruling then focused on the exceptions where Directive 2001/83/EC does not apply to preparations by pharmacies. For the exceptions in relation to *magistral formulae* as included in article 3 point 1, the ECJ identified three cumulative requirements in the provision. First, the medicinal product needs to be prepared in a pharmacy. Second, it needs to be prepared in accordance with a medical prescription. Finally, the prescription needs to be for an individual patient. According to the ECJ, the requirements should be interpreted strictly which means that the medicinal product should be prepared in accordance with a medical prescription that needs to be issued by a physician for a specific patient in advance, that is before the medicinal product is prepared for that patient.

The exception for *officinal formulae* in article 3 point 2 also contains three cumulative requirements. First, the medicinal products must be prepared in a pharmacy. Second, the medicinal products should be prepared in accordance with the prescriptions of a pharmacopoeia. Finally, the medicinal products should be intended to be supplied directly to the patients served by the pharmacy in question. The latter means, as the ECJ clarified, that a medicinal product must be supplied directly by the pharmacy which prepared it to the patients supplied by that same pharmacy. Consequently, the exception of article 3 point 2 does not allow pharmacies to supply *officinal formulae* to other pharmacies.

The ECJ provided a strict interpretation of the exceptions to the Directive 2001/83/EC, thereby limiting the opportunity for pharmacy preparations, but it did not rule on the facts of the specific case before the Swedish court. Therefore, it was up to the Swedish court to ascertain whether the conditions for application of article 2 and article 3, points 1 or 2 of Directive 2001/83/EC were satisfied. Furthermore, it should be borne in mind that if Directive 2001/83/EC is not applicable, then this allows for member states to establish national regulations in the matter. These regulations may, for example, include that national authorisations are required for pharmacy preparations.

Novartis versus Apozyt GmbH

Another interesting ECJ case in relation to pharmacy preparations is *Novartis versus Apozyt GmbH*.[9] Novartis holds the marketing authorisation for the medicinal product Lucentis (ranibizumab) for the treatment of the "wet" type of age-related macular degeneration (ARMD), a common form of age-related loss of vision. The recommended dose for Lucentis is a single injection of 0.5 mg into the eye. The procedure should be carried out under aseptic conditions. The syringe and the vial are approved for single use only. However, the prefilled syringe contains more than the recommended dose. Therefore when preparing the injection, the physi-

cian must expel the excess volume. Meanwhile, Avastin (bevacizumab) is a cancer medicine available as a concentrate that is made up into a solution for infusion (drip into a vein) of Roche Pharma AG, which is not a party to the main proceedings. However, Avastin has been used to treat ARMD off-label already before the marketing authorisation of Lucentis. For reasons related to cost, the off-label use of Avastin has been continued thereafter.

Apozyt is a company that fills syringes with Lucentis and Avastin. These syringes, which contain the exact amount needed for one injection, are dispensed to pharmacies. Apozyt's products are much cheaper because they can fill more syringes with the content of one vial of Lucentis or Avastin. In a court case between Novartis and Apozyt GmbH in Germany, the German court referred questions to the ECJ about the interpretation of EU regulations.

It is interesting that the ECJ did not assess, to what extent the products of Apozyt were allowed under the exceptions for pharmacies preparations. The ECJ considered that Apozyt did not need a marketing authorisation for filling syringes for injection with the medicines of Lucentis and Avastin as long as they met the following conditions: The filling of the syringes should not result in any modification of the medicinal product; the filling occurs only on the basis of individual prescriptions; and the injection is administered by the physician who prescribed the medicine. Under those circumstances, the activities could not be equated with a new placing on the market of a medicinal product as included in the first pillar of EU regulation described above.

This verdict of the ECJ clarified the need of a marketing authorisation. The case also related to the need for a manufacturing licence, but that will be discussed in section 2.2.4.

2.2.2 Specialties

Member states may, according to article 5 (1) of Directive 2001/83, exclude medicinal products from the provisions of the Directive. Medicinal products provided on the basis of article 5 (1) are also known as specialties. They may include medicinal products imported from other countries or medicinal products manufactured for a specific patient. However, article 5 (1) contains a number of requirements. First, the exception should be in accordance with the legislation in force in the member state. Second, the exception should be intended to fulfil special needs. Moreover, the medicinal products should be supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised health care professional and for use by his or her individual patients under the professionals' direct personal responsibility. Consequently, these specialties are medicines that are prescribed on a named-patient basis by a healthcare professional.

The ECJ has once again clarified the meaning of the provision and also outlined the scope of the exception for specialties.

European Commission versus the Republic of Poland

The medicines act in Poland stated that no marketing authorisation was required for medicinal products imported from other member states if those medicinal products contained the same active ingredient, the same concentration and the same dosage form but had a lower price than the medicinal products authorised in Poland. In the case the European Commission versus the Republic of Poland,[10] the European Commission (EC) held the position that the policy of Poland was contradictory to the requirement for a marketing authorisation in article 6 (1) of Directive 2001/83/EC, while Poland argued that the provision in their national law was based on the aforementioned exception provided in article 5 (1) of the Directive.

The verdict of the ECJ stated that the substantive rule was that a medicinal product may only be placed on the market if a marketing authorisation has been issued. The exceptions should be interpreted restrictively and the application must remain exceptional in order to preserve the practical effect of the marketing authorisation procedure.

The ECJ subsequently explained the meaning of a 'special need' and a 'bona fide unsolicited order' in article 5 (1). Special needs' "applies only to individual situations justified by medical considerations and presupposes that the medicinal product is necessary to meet the needs of the patient."[11] A 'bona fide unsolicited order' means "the medicinal product must have been prescribed by the doctor as a result of an actual examination of his patients and on the basis of purely therapeutic considerations."[12]

Furthermore, as the ECJ reasoned, the exception for specialties "can only concern situations in which the doctor considers that the state of health of his individual patients requires that a medicinal product be administered for which there is no authorised equivalent on the national market or which is unavailable on that market."[13] Special needs do not exist in cases where there are already authorised medicinal products available on the national market with the same active substances, the same dosage and the same form. It is interesting that financial considerations did not amount to a special need.

For pharmacy practice, it should be borne in mind that the exception for specialties does not apply to cases where an authorised medicinal product with the same active ingredient, the same concentration and the same presentation form, is available. The exception can only be justified by the special needs of the patient and not by financial considerations.

2.2.3 Compassionate use program

The third exception concerns the compassionate use program, which is established in article 83 of Regulation (EC) No 726/2004. It constitutes an exception from the prohibition to market medicinal products without a marketing authorisation as in article 6 of Directive 2001/83/EC. Member states may, for compassionate reasons, make a medicinal product available for human use to a group of patients with a chronic or seriously debilitating disease, or whose disease is considered to be life-threatening, and who cannot be treated satisfactorily by an authorised medicinal product. The medicinal product should have access to the centralised marketing authorisation procedure in Regulation (EC) No 726/2004. This exemption can only apply to medicinal products that are the subject of an application for a centralised marketing authorisation at the European Medicines Agency (EMA) or that are undergoing clinical trials. Member states are not obliged to implement the compassionate use option programme in their national laws. However, if they decide to do so, then they have to comply with the requirements of Article 83 of Regulation (EC) No 726/2004.

2.2.4 Manufacturing licence

The last exception concerns a manufacturing license. Article 40 (2) Directive 2001/83/EC states that a manufacturing licence is not required for preparation, dividing up, changes in packaging or presentation where these processes are carried out, solely for retail supply, by pharmacists in dispensing pharmacies or by persons legally authorised in the member states to carry out such processes. This exception for pharmacies applies regardless of the availability of equivalent authorised medicinal products.

The case of *Novartis versus Apozyt* is also relevant here because, besides the need for a marketing authorisation discussed above there was also the question of whether a manufacturing licence was required for Apozyt. The German government argued that such an authorisation would not be required since it had established an exception under the aforementioned specialties provision. However, as discussed earlier, that exception only applies in cases where no equivalent product is available. This condition had not been fulfilled in the case of Apozyt's product based on Lucentis, while it may apply in regard to Avastin.

Neither is a manufacturing licence required for the preparation of syringes with Lucentis so long as these processes are carried out, solely for retail supply, by pharmacists in dispensing pharmacies. Whether those conditions are fulfilled is for the national courts to decide. Consequentially, the acceptability of the activities carried out by Apozyt is largely dependent upon national legislation relating to the profession of the pharmacist, the implementation of the specialties regulation and the requirements concerning pharmacy preparations in the practice of the member states.

3. The EU regulation on medicinal products and the Resolution concerning pharmacy preparation

In the EU, as explained above, medicinal products are regulated by Directive 2001/83/EC and Regulation (EC) No 726/2004. This EU legislation offers some space for pharmacy preparations, but only under certain strict conditions as defined in these regulations. Pharmacies specialised in preparation may not, however, always fulfil these strict conditions.

In the case that Directive 2001/83/EC does not require a marketing authorisation for the medicinal product, member states are allowed to establish national regulations for pharmacy preparations. These regulations may, for example, stipulate that national authorisations are required for pharmacy preparations. For pharmacy preparations, which are outside the scope of Directive 2001/83/EC, the Resolution provides guidance to the member states.

The Resolution, which is adopted by 37 member states, provides a means of establishing standards for safety and quality assurance for pharmacy preparations. The Resolution is not legally binding, but expresses the wish of the member states to have the option of centralised pharmacy preparation and to standardise the safety and quality standards for pharmacy preparations. It helps pharmacists to determine what adequate standards of quality are. Before preparation, a risk assessment should always be carried out by the pharmacist in order to define the level of the quality assurance system which should be applied to the preparation process of the medicinal product. The Resolution recommends that the Good Manufacturing Practice (GMP) Guidelines[14,15] are used as a reference for an appropriate quality system for "high-risk preparations", and that the PIC/S GPP Guide[16] be used for "low-risk preparations". The Resolution also discusses multiple other elements that may be incorporated into a safety and quality assurance system for pharmacy preparations. These include: a product dossier containing product-specific quality properties and site-specific manufacturing conditions; criteria for a marketing authorisation; labelling; compliance with pharmacopoeial requirements; authorisation for pharmacies or licences for companies making preparations for pharmacies; transparency and safety; communication and information to patients; and distribution of pharmacy preparations.

The centralisation and specialisation of pharmacy preparation has occurred in multiple member states, whereas, at the same time, an increasing number of pharmacies lack the facilities and competence to fulfil the quality standards for the preparation of medicinal products. Some pharmacies may have discontinued the preparation of magistral and officinal medicinal products and, instead, use the services of pharmacies specialised in pharmacy preparation. Specialised pharmacies are usually in a better position than pharmacies that prepare medicinal products on a small scale. They are better able to invest in quality assurance and safety

standards such as those related to personnel, premises and equipment. Member states have, indeed, established national regulations with regard to specialised pharmacies and have taken the safety and quality assurance elements of the Resolution into account. This is presented in a separate article. [4]

4. Discussion and conclusions

The system of European regulation of medicinal products has two pillars: the marketing authorisation of the medicinal product and the manufacturing licence. The EU legislation on medicinal products – Directive 2001/83/EC and Regulation No (EC) 726/2004 – provides a number of exceptions through which the EU legislation or specific provisions, for example, the requirement for a marketing authorisation, do not apply. The ECJ has provided an interpretation of the legislation which established that a wide scope of products is subject to the EU legislation, while, in turn, restricting the products subject to the exceptions. Their interpretation of Directive 2001/83/EC limits the space for pharmacy preparations. It is questionable whether this interpretation takes into account the fact that the magistral formula and officinal formula are not available for multiple patients whose pharmacy has stopped pharmacy preparation. These non-preparing pharmacies subcontract this activity to pharmacies specialised in pharmacy preparation and dispensing.

The limited space for pharmacy preparations raises the question of whether the EU legislation Directive 2001/83/EC needs to be amended. Given that the ECJ restricts the products subject to the exceptions in the EU legislation, it is important to consider whether health care and the rights of patients are sufficiently guaranteed in cases where patient needs cannot be fulfilled by an authorised medicinal product manufactured by the pharmaceutical industry. Today, pharmacies may decide to make use of the services offered by pharmacies specialised in preparation to fulfil special patient needs. Pharmacies specialised in pharmacy preparation also fulfil an important role in the supply of medicinal products, for example, when the availability of an industrial product with a marketing authorisation has been interrupted or stopped altogether. However, the supply of medicinal products by specialised pharmacies to local pharmacies is not allowed on the basis of article 3 of Directive 2001/83/EC as has been demonstrated in the *Abcur v Apoteket* case. The exception of article 5 of that Directive with regard to 'specialties' might be an option to allow pharmacies specialised in the preparation of medicinal products to dispense their products, but, this is only if the conditions of article 5 are fulfilled. Whether article 5 is a real option that fits in with EU legislation needs further evaluation. If none of these exceptions apply, then the two pillar system of Directive 2001/83/EC is fully applicable. That means that a marketing authorisation of the medicinal product and a manufacturing licence for the pharmacy are required.

If the conditions in the definition of pharmacies' preparations in Directive 2001/83/EC are fulfilled, then the Directive does not apply and member states may establish national regulations for pharmacy preparations. The national regulations may be based on the standards for safety and quality assurance referred to in the Resolution including the situation in which there is external supply of medicinal products by specialised pharmacies to dispensing pharmacies. This may reduce the risk to patients associated with pharmacy preparation.

Previous research shows that there is large variation in the standards and policies regarding pharmacy preparations within Europe.[1] However, it is common practice throughout member states to allow pharmacy preparations for the treatment of patients for which no licensed medicinal product is available on the market.[4] Further evaluation is required to see whether the pharmacy preparations and the related national policies are in line with current EU legislation and the Resolution, and the consequences thereof.

If the practices concerning pharmacy preparation in European countries do not fit within current EU legislation, then there may be a real problem for individual patient care. We feel that there should be sufficient space for the preparation of medicines in pharmacies in order to accommodate individual patients' needs in Europe, provided that an authorised medicine does not exist or is unavailable on the market. Pharmacy preparations should be able to fulfil all special patient needs, including the needs of patients belonging to a pharmacy that has stopped preparation and that has subcontracted the pharmacy preparation to a pharmacy specialised in preparation. However, this subcontracting is, in our opinion, only in the interest of the patient under the condition that the pharmacy specialised in preparation fulfils all the safety and quality assurance elements mentioned in the Resolution.

Key messages

What is already known on this subject?

1. The European Union (EU) regulation determines under which conditions a marketing authorisation is required in order to place a medicinal product on the market and under which conditions a manufacturing and wholesale licence is required. However, EU regulation allows some exemptions such as for pharmacy preparations.
2. It is common practice throughout member states to allow pharmacy preparations for the treatment of patients for which no licensed medicinal product is available on the market. Since 2011, the member states of the Council of Europe are recommended to use the Council of Europe Resolution on quality and safety standards for pharmacy preparations for the special needs of patients.

What this study adds?

1. The article outlines the pillars of European Union (EU) regulation of medicinal products including the circumstances in which the EU regulation does not apply. It also provides insight into the recent interpretation of the European Court of Justice (ECJ) concerning the scope of EU regulation of medicinal products and the exceptions to it.
2. Relevant standards for safety and quality assurance, such as the ones provided in the Resolution, are needed in Europe in order to protect patient rights and to avoid risks associated with pharmacy preparations.
3. In the case Abcur AB versus Apoteket, the ECJ provided a strict interpretation of the exceptions to the Directive 2001/83/EC, thereby limiting the opportunity for pharmacy preparations. If the practices concerning pharmacy preparation in European countries do not fit within current EU legislation, then there may be a real problem for individual patient care.

Acknowledgements

Delegates of the countries of the Council of Europe.

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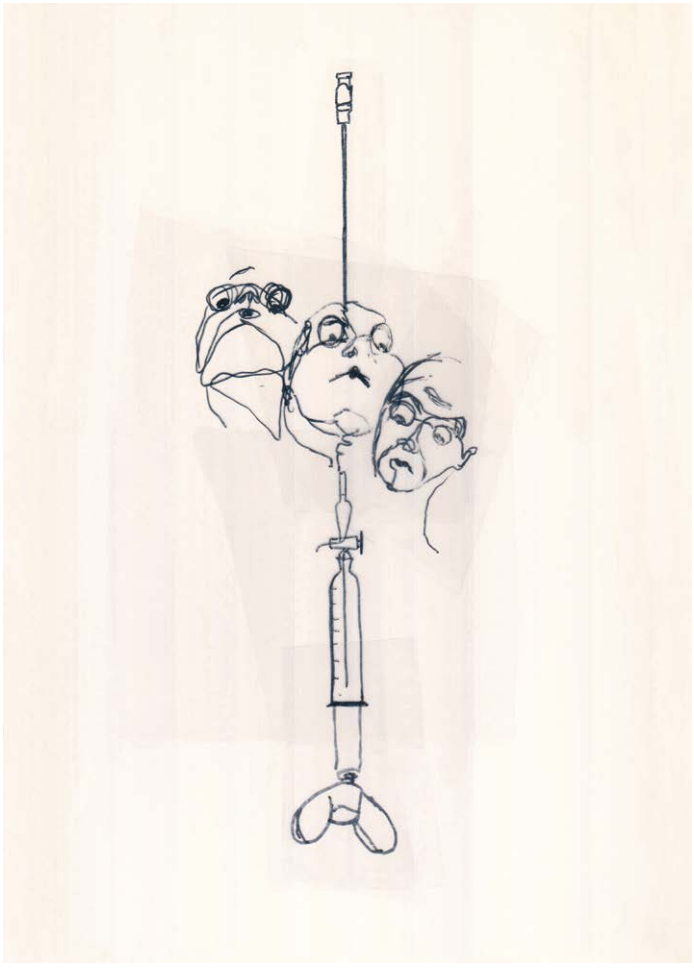

Chapter 5

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 (e.g. 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 which 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 (EDQM), 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 (EAHP) 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 (e.g. 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 health care establishments introduces risks for patients' safety. Adequate reconstitution of medicinal products is considered to be of crucial importance for patient safety by national authorities, health care 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 37 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 GMP[2] 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 (API) 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 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, etc[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 favorable nutrient medium for microorganisms may be a causative factor for a high number of infectious complications[22]. There have also been fatalities with Parenteral Nutrition (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 and 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 survey[26] 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 Resolution[1] on pharmacy preparation, which included some recommendations and an outlook to further work on reconstitution of parenteral medicines.

Resolution[1] 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.

The Committee of Ministers has now adopted Resolution CM/Res AP(2011)1[1] 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, a EU Directive) and national frameworks will be taken into account by the member states.

The Resolution[1] 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 pa-

tient 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 US[28-30].

Reconstitution paragraph in Resolution[1]

In chapter 9 of the Resolution[1] specific reference is made to the reconstitution of medicinal products in health care 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 health care 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, clinics etc.

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 Resolution[1] recommended that national authorities should develop, in co-operation 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 health care 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 health care 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 Resolution[1] recommends that national authorities should develop, in co-operation 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 health care establishments.

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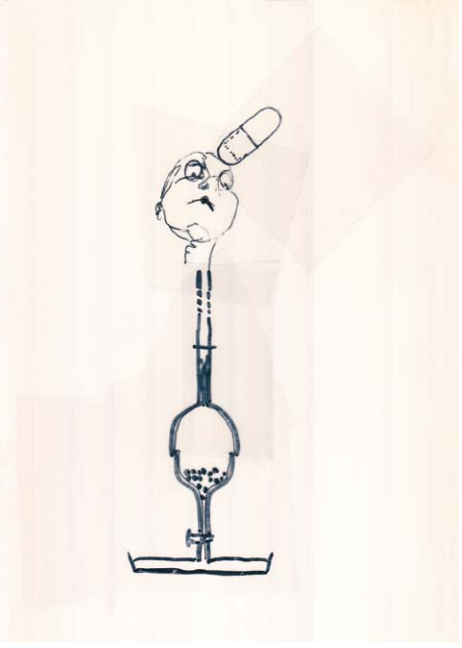

Chapter 6

Inspectorate surveillance of Preparing and Distributing Pharmacies in the Netherlands

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Abstract:

Introduction and objective

The preparation of medicines in pharmacies is essential for accommodating the individual needs and medical conditions of patients in Europe and beyond. This article describes the state of pharmacy preparation in preparing and distributing pharmacies (PDPs) in the Netherlands.

The Medicines Act in the Netherlands is based on European Union (EU) Directive 2001/83/EC which forbids a PDP from preparing and distributing unlicensed medicinal products to dispensing pharmacies.

In order not to obstruct patient care, the Dutch Inspectorate has sent a Circular Letter on large-scale preparation to all Dutch pharmacists. This Circular describes the qualitative conditions that must be fulfilled by the PDPs.

The aim of this study was to assess the overall compliance of Dutch PDPs with the conditions of the Circular. These conditions are: an absence of licensed pharmacotherapeutic alternatives, rational pharmacotherapy, a product dossier for all products, and compliance with Good Manufacturing Practice (GMP).

Methods

PDPs are obliged to fulfill the conditions of the Circular. If PDPs do not fulfill these conditions, then they have to stop preparing and distributing medicinal products.

A questionnaire was sent to all Dutch pharmacies to get information about the number of PDPs and the number of pharmacies served by each PDP.

The instrument that was used in this observational study to assess the compliance of the PDPs with all conditions of the Circular is described.

Results

The results of the inspections until now show that on November 1st, 2014, 18 out of 21 PDPs fulfilled the four conditions of the Circular. Only minor deficiencies were found with 3 out of 21 PDPs. Twenty out of the 21 PDPs visited fulfilled the condition concerning the absence of pharmacotherapeutic alternatives and 19 out of 21 PDPs visited complied with the condition of rational pharmacotherapy. Nineteen out of the 21 PDPs visited fulfilled the Circular condition that a product dossier was available for all products. All of the 21 PDPs visited complied with GMP.

Regular visits, at least every three years, were performed by the Inspectorate to check the compliance of the PDPs with the Circular. The publication of the inspection reports on the website of the Inspectorate allowed, probably, many PDPs to be better prepared. The inspection visits showed that the PDPs have invested in compliance with the conditions of the Circular.

Conclusions

Most of the PDPs fulfilled the requirements of the Circular. The Inspectorate is in consultation with the Ministry of Health, Welfare and Sport about how to proceed with the question of PDPs and the conditions they have to fulfill. Recent European case law will have to be taken into account.

1. Introduction and objective

The Medicines Act and the Circular for preparing and distributing pharmacies.

The Medicines Act in the Netherlands is based on European Union (EU) Directive 2001/83/EC which forbids an unlicensed medicinal product being prepared and distributed by a preparing and distributing pharmacy (PDP). PDPs prepare medicinal products in their pharmacy and distribute these products to a dispensing pharmacy. The dispensing pharmacy receives the prescription for a patient and provides the pharmacy preparation, made by another pharmacy, to the patient.

In the Netherlands, a pharmacy consists of premises that are coherent and connected[1]. By law, it is obliged to have a pharmacy at each address where a stock of medicines is kept. Therefore, a PDP that prepares and distributes medicinal products to dispensing pharmacies belonging to the same legal entity has to fulfill the conditions of the Circular.

There are, however, patients that need a pharmacy preparation because there is no adequate licensed alternative medicinal product available on the market[2]. Examples are patients who are allergic to lactose or other ingredients of the registered product, or patients who need a lower dose than the registered dose of that medicinal product. Strict reinforcement of the Medicines Act by the Inspectorate is not considered an option because this would impede the availability of these essential medicines.

The need of the patient for a pharmacy preparation due to a lack of a licensed alternative medicinal product has already existed for many years. In 2002, the Inspectorate issued a Circular which obliged the PDPs to be in the possession of a medical prescription in order to demonstrate an individual patient's need. Apart from this obligation, there were no specific criteria applicable to PDPs. The general criteria applicable to pharmacies also applied to PDPs.

Since 2007, the PDPs have been permitted by the Inspectorate by means of a new Circular[3]. The conditions of this new Circular were necessary because the large-scale pharmacy preparations in PDPs were substantially different from small-scale pharmacy preparations. Its conditions only applied to PDPs preparing medicines for dispensing pharmacies. This Circular was supported in parliament by the Ministry of Health, Welfare and Sport. It is obliged to fulfill the conditions of the Circular. If the PDPs do not fulfill the conditions of the Circular then they have to stop the preparation and distribution of their medicinal products.

The trend is towards pharmacies stopping with pharmacy preparation and transferring these activities to PDPs[2]. In general, routine preparation on a large or a

more frequent scale, with the use of specific equipment and expertise, provides a better product quality assurance.

The Inspectorate monitors these developments in order to ensure that the principle of market authorization for medicinal products, as described in EU Directive 2001/83/EC and implemented in the Dutch Medicines Act, is not undermined. This Act[4] requires that medicinal products that are available on the Dutch market are evaluated in advance for their efficacy, safety and quality by the Dutch Medicines Board or European Medicines Agency and that a marketing authorization is granted, if appropriate, for these medicinal products. This Act[5] also requires that medicinal products are prepared under a manufacturing license. However, limited exceptions exist. One such is the preparation and dispensing of the medicinal products on a small scale by a pharmacist in his or her pharmacy[5,6]. Usually, the larger scale of a PDP excludes it from this exception, which is geared towards small-scale preparation in a pharmacy.

Conditions for PDPs

In the Circular the Inspectorate explains that PDPs are obliged to fulfill the following conditions:
a. No licensed alternative medicinal product is available on the market;
b. The pharmacotherapeutic rationale is demonstrated;
c. Product dossiers (PDs) are available for all products;
d. Production complies with Good Manufacturing Practice (GMP).

Advertising is forbidden

The Circular[3] states that neither the PDP nor the dispensing pharmacy is allowed to advertise for unlicensed medicines. This is a logical consequence of EU Directive 2001/83/EC which is implemented through the Dutch Medicines Act[7].

Compliance with these conditions is assessed during inspections by the Inspectorate. If these conditions are not fulfilled by the PDP then the PDP has to stop the preparation and the distribution of its medicinal products.

Objective of the article

The aim of this study was to assess the overall compliance of the PDPs with the conditions of the Circular. These conditions are: an absence of licensed pharmacotherapeutic alternatives (PA), rational pharmacotherapy, a PD for all products, and compliance with GMP. Regular visits were performed by the Inspectorate to check the compliance of the PDPs with the Circular. PDPs not complying were re-

visited until they complied. If they did not comply during repeated visits, then they had to stop their preparation and distribution activities.

This article describes the results of the Dutch Health Care Inspectorate programme operating since 2007 for each of the conditions of the Circular, including such measures as enforcement.

2. Consultations with professional associations

Consultations between the Inspectorate and the associations of pharmacies, including hospital pharmacies.

The Inspectorate has conducted periodic consultations with the associations of pharmacies, including hospital pharmacies, which began immediately after the Circular came into force. These consultations were aimed at the details of the conditions of the Circular and its implementation.

The conditions of the 2007 Circular were new for the PDPs. Guidance was therefore needed at the professional level in order to specify further how to fulfill these conditions systematically. The GMP condition was an example of one of the new conditions. The pharmacists and other personnel in the PDPs had to develop expertise in GMP. The expertise of the PDPs had to be developed too for the other conditions.

The associations of pharmacists have developed guidelines and tools[8] for pharmacists on:

1. How to investigate and document the availability of registered PA and to show evidence that none of these alternatives is available before the pharmacist makes the pharmacy preparation. PA investigation.
2. How to perform investigations on the pharmacotherapeutic rationale and to show documented evidence for the need for the pharmacy preparation. Pharmacotherapeutic rationale (PT) investigation.
3. How to compile an adequate PD, for stock preparations and for standardized individual preparations. PD investigation.
4. How to comply with GMP.

Frequently asked questions and answers, published by the Inspectorate

There was a need, expressed by community pharmacists and hospital pharmacists, for further clarification of the conditions of the Circular. Therefore the Inspectorate has put answers to frequently asked questions (FAQs) on its website[9].

3. Methods

Questionnaire aimed at achieving transparency

Because there is no notification requirement for PDPs in the Dutch Medicines Act, the Inspectorate has sent a questionnaire to all pharmacies in 2007 and 2008 asking them about the status of their preparation activities, as far as it concerned the distribution of unlicensed pharmacy-made medicines to other pharmacies. The results of the questionnaire were used to perform risk-based inspections. The PDPs that served the highest number of dispensing pharmacies were given the highest priority when arranging visits. The reason for this is that, in the case of a possible product defect, the consequences are higher if the product is distributed to more pharmacies. The questionnaire was sent in 2007 and 2008 to 2,480 Dutch pharmacies, including 81 hospital pharmacies. The response to the questionnaire was 99% for hospital pharmacies and 94% for community pharmacies. There were 379 PDPs:

- 7 pharmacies (2%) distributed their products to more than 100 other pharmacies.
- 8 pharmacies (2%) to 51-100 other pharmacies.
- 9 pharmacies (2%) to 21-50 other pharmacies.
- 23 pharmacies (6%) distributed the products to 11-20 other pharmacies;
- The remainder of the PDPs (88%) distributed their products on a smaller scale to fewer than 10 pharmacies.

Twenty-eight of these 47 (60%) pharmacies were hospital pharmacies.

Surveillance by the Inspectorate.

The Inspectorate has been responsible for overseeing PDPs compliance with the conditions of the Circular since 2007. To perform the visits, the Inspectorate has developed an instrument to assess whether the PDPs fulfilled the four conditions of the Circular. The assessment of the Inspectorate was based upon an instrument that assessed PA, PT and PD (A-C) and GMP (D):

A. The documentation of the PA investigation;

The assessment by the Inspectorate of the PA investigations carried out by the PDP consisted of three items to be scored. These are:

1. The procedure for assessing PA.
2. The criteria for the PA included in the procedure;
3. The investigation of licensed PA based on a random check by the Inspectorate of the forms for some selected products;

The score for each of these three items could vary from 1 to 4, as it is shown in the table below:

1 (absent)	The standard is absent; the standard is not followed and is not available in a documented form.
2 (available)	The standard is demonstrably available, but it is not followed consistently. The written procedures are available but not all employees involved are aware of the procedures.
3 (operational)	The standard is operational and is followed consistently. All employees working with the standard are aware of the written procedures but a regular evaluation or adjustment does not take place.
4 (guaranteed)	The standard is guaranteed and followed consistently. The employees are well aware of the written procedures. Moreover, regular evaluation takes place and, if needed, adjustment.

Based on observations and information gained during the visit to the PDP, the Inspectorate assessed each item to be scored as adequate if that item scored at least 3. A score of 4 is the level of quality to be strived for, but this score was not always assessed during the inspection visits.

The result for the Circular's condition relating to PA was assessed as sufficient if a score of at least 3 was given for each of the three abovementioned items to be scored. This means that the PDP has clear procedures and instructions on how to perform the PA investigation and that the PDP follows these in daily practice.

B. The documentation of the PT investigation;

The assessment by the Inspectorate of the PT investigations carried out in the PDP consisted of three items to be scored. These are:

1. The procedure for assessing the pharmacotherapeutic rationale.
2. The assessment of the pharmacotherapeutic rationale for a stock preparation, based on a random check by the Inspectorate of the forms relating to a sample of selected products.
3. The minimum requirement for the level of evidence for prepared stock preparations that were distributed to other pharmacies[10].

The score for each of these three items could vary from 1 to 4, as shown in the aforementioned table.

The result for the Circular's condition relating to PT was assessed sufficient if a score of at least 3 was given for each of the three items. This means that the PDP has clear procedures and instructions on how to perform the PT investigation and that the PDP follows these.

C. The PDs, PD investigation;

The assessment by the Inspectorate of the PDs consisted of the following items to be scored:

1. The procedure for the assessment of the technical and pharmaceutical aspects.
2. The procedure for PDs.
3. The format for PDs.
4. The assessment of the quality of the PD.
5. The availability of PDs for the products made, based on a random check by the Inspectorate of the PDs relating to a sample of selected products.

The score for each of these items could vary from 1 to 4, as shown in the aforementioned table.

The result for the Circular's condition relating to PDs was assessed sufficient if a score of at least 3 was given for each of these items. This means that the PDP has clear procedures and instructions on how to make a product dossier and that the PDP follows these.

D. GMP

The Circular states that GMP compliance is one of the conditions for a PDP. All parts of GMP[11] had to be assessed during the inspection visits at the PDPs.

The deficiencies of the PDP concerning GMP were classified on the basis of the following definitions:

- critical deficiency:
  A deficiency which has produced, or leads to a significant risk of producing, a product which is harmful to the patient.
- major deficiency:
  A non-critical deficiency:
  which has produced, or may produce, a product, which does not comply with its product dossier;
  or
  which indicates a major deviation from EU GMP;
  or
  which indicates a failure to carry out satisfactory procedures for the release of batches;
  or
  a combination of several "other" deficiencies, none of which on their own may be major, but which may, together, represent a major deficiency and should be explained and reported as such;

- other deficiency:
  A deficiency, which cannot be classified as either critical or major, but which indicates a departure from good manufacturing practice.
  A deficiency may be "other" either because it is judged as minor, or because there is insufficient information to classify it as a major or critical.

The result for the Circular's condition GMP was assessed insufficient for the PDP if one critical deficiency was found or if there were more than 5 major deficiencies. GMP was assessed sufficient if there were 5 or fewer than 5 major deficiencies.

Advertising

The Inspectorate has investigated the websites of the PDPs and, if considered necessary, an advertising inspector was added to the inspection team. This was considered necessary if the website of the PDP contained elements of advertising[7].

Publication of inspection reports.

The inspection reports of all PDPs were published on the website of the Inspectorate (www.igz.nl) in accordance with a specific procedure communicated to the PDPs in advance.

4. Results.

There was a large variation in the types of PDPs which we visited, but nearly all those who dispensed their products through at least ten dispensing-only pharmacies, were inspected.

However, changes in the status of the PDPs occur continuously, which means that the planning of the visits has to be adapted regularly.

The results of the Inspectorate's system surveillance

4.1. Compliance with the conditions of the Circular relating to the whole system.

The Inspectorate had to perform repeated inspections since the results of the first inspection visits of the PDPs were disappointing because they did not comply with the conditions of the Circular. Moreover, the capacity for these inspections had to be increased. In the meantime, the consultations with the professional associations continued as normal. During these first inspection visits enforcement measures were taken in one PDP. In this PDP risks were seen for patient care because essen-

tial GMP safety measures for the preparation of sterile products were assessed as insufficient. Therefore, the sterile preparations of this PDP were halted temporarily until the PDP had implemented all the necessary safety measures.

In the years 2012 – 2014, the Inspectorate performed repeated inspections at most of the PDPs that did not comply with the conditions of the Circular. In total 34 PDPs were visited. Twenty-one PDPs complied or nearly complied with the Circular, as it is shown in the Table below:

Table with the results of the inspections of PDPs

PDP	circular	NC		PA	PT	PD	GMP
1	1			1	1	1	1
2	1			1	1	1	1
3	1			1	1	1	1
4	1			1	1	1	1
5	1			1	1	1	1
6	1			1	1	1	1
7	1			1	1	1	1
8	1			1	1	1	1
9	1			1	1	1	1
10	1			1	1	1	1
11	1			1	1	1	1
12	1			1	1	1	1
13		1		0	0	1	1
14	1			1	1	1	1
15	1			1	1	1	1
16	1			1	1	1	1
17		1		1	1	0	1
18	1			1	1	1	1
19	1			1	1	1	1
20	1			1	1	1	1
21		1		1	0	0	1
totaal	**18**	**3**	**21**	**20**	**19**	**19**	**21**

Code 1 - compliance.
Code 0 - non-compliance.
NC - 'nearly complying'.
PA - 'pharmaceutical alternatives'.
PT - 'pharmacotherapeutical rationale'.
PD – 'Product dossiers'.
GMP - 'Good Manufacturing Practice'.

The status concerning the 34 PDPs on November 1st, 2014 was as follows:

- the Table shows that eighteen PDPs complied with all conditions of the Circular. Three PDPs complied with GMP, but there were some minor deficiencies concerning the other conditions of the Circular. These PDPs will be inspected again until they fulfill all the conditions of the Circular;

- One PDP distributed only licensed products, which were reconstituted at the PDP for direct use by the patient, in a small region. It was difficult to assess, therefore, whether the conditions of the Circular applied;
- For another PDP, the inventory did not predominantly consist of medicinal products, so an inspection had to be planned together with the Netherlands Food and Consumer Product Safety Authority;
- Ten PDPs had stopped distribution of the medicinal products to dispensing pharmacies because they could not fulfill the conditions of the Circular or because they considered it not feasible to make the necessary investments. Verification visits were performed by the Inspectorate in order to check whether these PDPs had, in fact, stopped distribution;
- One PDP prepared its products through a company which did not possess a manufacturing license. This is forbidden by the Dutch Medicines Act, for which reason the Inspectorate took enforcement measures to stop this practice.

On 1 November 2014, there were 13 new PDPs. The reports of these inspection visits were not included in this observational study because the reports were not yet finished (seven PDPs) or because the visits were not yet carried out (six PDPs).

These results show that 18 out of 21 PDPs complied with all conditions of the Circular. Only three of these PDPs required more than one inspection visit. Only minor deficiencies were found with 3 out of 21 PDPs. The publication of the inspection reports on the website of the Inspectorate allowed, probably, many PDPs to be better prepared. The inspection visits showed that the PDPs have invested in compliance with the conditions of the Circular.

4.1.1. The conditions of the Circular concerning PA and PT investigations of the system.

The PDPs are obliged to document the results of their PA and PT investigations for all products. On 1 November, 2014, 20 out of the 21 PDPs visited fulfilled the PA condition and 19 out of 21 PDPs visited complied with the PT condition. The details about this requirement of the Circular will be presented in a separate publication[10].

4.1.2. The conditions of the Circular concerning the systematic use of a product dossier (PD).

The PDPs should have a PD available for all their products, stock preparations and standardized individual preparations, in order to document the quality by design of the pharmacy preparation. The topics to be covered in a product dossier are described on the website of the Inspectorate and in the resolution on pharmacy preparation of the Council of Europe[2, 9].

As of 1 November, 19 out of the 21 PDPs visited fulfilled the PD condition of the Circular. For two PDPs, significant improvements were made concerning the PDs, but the documentation still showed deficiencies that required further improvement.

At the request of the Inspectorate, the National Institute for Public Health and the Environment (RIVM) has performed descriptive research concerning the quality of the PDs[12]. Its report states that the quality of the PDs and the information contained in them is, in general, reasonably good. One of the recommendations of the RIVM report is to make a fixed format for the content of the PDs since a large variation was found in the content of the dossiers, especially in PDPs among the community pharmacies. In addition, the documentation should demonstrate that all items of the PD, such as validations and stability data, have been completed. There is, therefore, a clear basis for the overall conclusion that the PD of a particular product of a PDP is complete before distribution takes place to dispensing pharmacies.

4.1.3. The conditions of the Circular Letter concerning GMP.

As of November 1st, all of the twenty-one PDPs visited complied with GMP.

5. Discussion

Current situation

There is a broad consensus in the Netherlands concerning the conditions of the Circular[8]. The GMP condition seemed the most difficult requirement to comply with, but all of the 21 PDPs visited had complied in 2014.

The initial results in 2011 had been disappointing, but in 2014 the inspections showed a clear improvement in the compliance with the conditions of the Circular. The progress made was possible due to the efforts of the different stakeholders. These were that:

- The PDPs have invested in compliance measures, in many cases hiring external experts to accelerate the process;
- The associations of hospital pharmacies and community pharmacies have developed tools and other information materials to support pharmacies;
- The Inspectorate has increased the capacity of the inspection programme. It performed repeated inspections until the required level of quality was achieved. The Inspectorate took reinforcement measures where needed.

Additional findings during the inspections

GMP is considered an appropriate quality standard for pharmacy preparation in PDPs[2]. The risks of possible product defects that might occur at PDPs and its implications for the patients being treated are substantial. Emphasis should therefore be given to all efforts to prevent these risks.

Given the character and the scale of the pharmacy preparations, there may be situations that GMP cannot be declared applicable. This could for example be the case if the preparation in the PDP of a specific medicinal product is on a small scale. If GMP has not been declared as a clear requirement for a given situation in a PDP, then the Dutch Pharmacy Standard[13] could, if necessary, be considered to be an appropriate standard. However, this is only for that specific situation and could here be backed up by the three other conditions contained in the Circular.

Some points of attention have been addressed during and after the inspection visits.

1. Product defects and recalls.
   In general, PDPs do not possess a system for addressing product defects, quality complaints, mistakes and other signals warning of possible problems with their products. There have been recalls by PDPs in the case of deviations from the product dossiers, but, given the relatively low number of recalls, the awareness around this topic may have to be increased. Internal exercises at PDPs to test their ability to trace either batch and lot numbers or the dispensing pharmacies to which the products were distributed, and then to recall the products, are of crucial importance.
2. Pharmacovigilance.
   There may be products distributed by the PDP where the balance between efficacy and safety is questionable. Therefore it is important that dispensing pharmacies that receive medicinal products from the PDP report safety problems to the PDP. The PDP should be capable of gathering and evaluating information about their products such as that concerning adverse events or warning signals in order that appropriate measures can be taken in case of safety problems.
3. Responsibilities
   The responsibilities of the pharmacies concerned here, the PDPs and the dispensing pharmacies, are, in general, laid out in a contract. However, the description of the different tasks and responsibilities such as reporting adverse events and product defects, the surveillance of medication and with regard to patient information, needs attention.

6. Conclusions

A circular is a temporary measure usually only accepted in anticipation of a new law. However, there is a dilemma here. On the one hand the Dutch Medicines Act and EU Directive 2001/83/EC, on which it is based, aims to protect public health by means of a system of marketing authorizations and manufacturing licenses. On the other hand, the preparation of unlicensed medicines in pharmacies is indispensable for patients with special needs, in particular if an appropriate licensed medicine is not available on the market.

PDPs have been permitted in the Netherlands since 2007 so long as they fulfill the conditions of the Circular[3]. The Circular allows, under strict conditions, the preparation of unlicensed medicinal products in a preparing pharmacy and then their distribution to a dispensing pharmacy.

The Inspectorate has many different roles in the implementation of the conditions of the Circular. It has had to clarify the new conditions of the Circular in cooperation with the professional associations. It has also been required to ensure the implementation of the conditions by means of revisiting PDPs who do not comply with the Circular. Where needed, enforcement measures were taken by the Inspectorate, in particular in PDPs where the risks for patient care were identified. Publishing the results of the inspection on the Inspectorate's website has helped to create transparency about the conditions to be fulfilled by the PDPs. All these actions by the Inspectorate have helped ensure that PDPs stop preparing and distributing medicinal products to dispensing pharmacies, if the PDPs do not fulfill these conditions.

The results of the inspections until now indicate that most of the PDPs fulfill the conditions of the Circular. Compliance of the PDPs with these conditions was checked by the Inspectorate through regular visits. However, changes in the status of the PDPs occur continuously, which means that the planning of the visits has to be adapted regularly.

The Inspectorate is in consultation with the Ministry of Health, Welfare and Sport about how to proceed with the question of PDPs and the conditions they have to fulfill. Recent European case law will have to be taken into account[14].

Key Messages

What is already known on this subject:

- The Medicines Act in the Netherlands is based on European Union (EU) Directive 2001/83/EC which forbids an unlicensed medicinal product being prepared and distributed by a preparing pharmacy (preparing and distrib-

uting pharmacies (PDPs)) to a dispensing pharmacy - that is one which dispenses the medicinal product to the patient.

- There are, however, patients that need a pharmacy preparation because there is no adequate licensed alternative medicinal product available on the market.
- Since 2007, the PDPs have been permitted by the Inspectorate by means of the Circular. This Circular allows, under strict conditions, preparation of unlicensed medicinal products in a preparing pharmacy and distribution of these products to a dispensing pharmacy.
- The PDPs are only permitted if they fulfill the strict conditions of the Circular: absence of licensed pharmacotherapeutic alternatives; rational pharmacotherapy; compilation of a product dossier; compliance with GMP.

What this study adds

- The results of the inspection programme of the Dutch health Care Inspectorate show that most of the PDPs fulfill the conditions of the Circular at a systematic level.
- The Inspectorate is in consultation with the Ministry of Health, Welfare and Sport about how to proceed with the question of PDPs and the conditions they have to fulfill. Recent European case law concerning the interpretation of the EU Directive 2001/83/EC will have to be taken into account.

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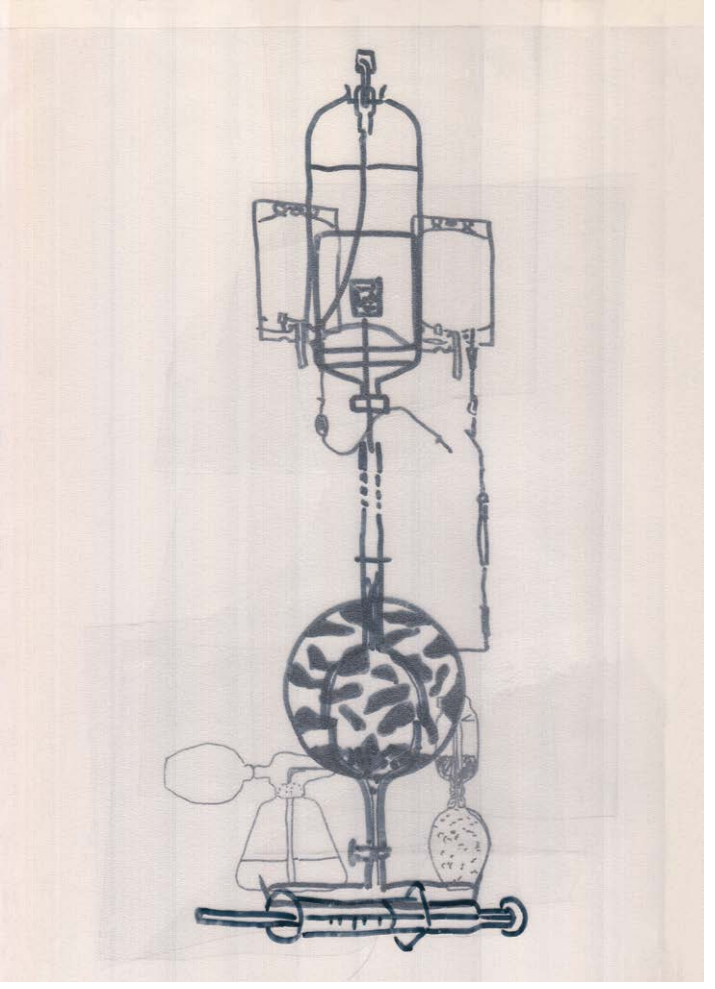

Chapter 7

Pharmacotherapy of unlicensed medicines prepared and distributed by Dutch pharmacies

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Abstract

Introduction and objective
In the Netherlands, Preparing and Distributing Pharmacies (PDPs) are taking over a large proportion of pharmacy preparations. PDPs prepare and distribute medicinal products to dispensing pharmacies. Many pharmacies have stopped pharmacy preparation. However, this contravenes the Dutch Medicines Act and the European Union (EU) Directive 2001/83/EC on which Dutch law is based. This is because the medicinal products of the PDPs are unlicensed and the PDP does not have a manufacturing license.
Methods
To solve the conflict with the Dutch Medicines Act, PDPs have since 2007 been permitted by the Dutch Health Care Inspectorate by means of a Circular Letter. This Circular describes the qualitative conditions that must be fulfilled by the PDPs.

The Circular's conditions state that the PDPs must perform verifiable investigations to assess the availability, or not, of licensed Pharmacotherapeutical Alternatives (PA investigations) and to assess the Pharmacotherapeutical rationale and the needs of the patient (PT investigations).
Results
Regular visits were performed by the Dutch Health Care Inspectorate to check the compliance of the PDPs with the Circular. This article describes the results of the these inspections for PA and PT investigations.
Conclusions
The results of the inspections until now show that almost all PDPs inspected complied with the PA and PT conditions of the Circular at system level. However, in a substantial proportion of cases the rationale of the pharmacy-made products is insufficient or insufficiently documented.

1. Introduction

The Medicines Act and the Circular Letter for preparing and distributing pharmacies (PDPs).

The Medicines Act in the Netherlands forbids the preparation and distribution of an unlicensed medicinal product by a PDP to a dispensing pharmacy. The latter pharmacy receives the prescription for a patient and provides the pharmacy preparation to the patient.

The Medicines Act in the Netherlands is based on European Union (EU) Directive 2001/83/EC. This Directive and thus the Medicines Act requires that no medicinal product may be placed on the market of a member state unless a marketing authorisation has been issued by the competent authorities of that member state[1]. The limited exceptions to this general rule are the magistral formula (any medicinal product prepared in a pharmacy in accordance with a medical prescription for an individual patient) and the officinal formula (any medicinal product which is prepared in a pharmacy in accordance with the prescriptions of a pharmacopoeia that is intended to be supplied directly to the patients served by the pharmacy in question)[1]. Although the scale of the operations of PDPs and the number of pharmacies they are supplying vary widely, these definitions of magistral - and officinal formula refer to pharmacy preparation on small scale, which does not usually correspond to the larger scale of a PDP[2]. This contravenes the Dutch Medicines Act because the medicinal products are unlicensed and the PDPs do not have a manufacturing licence[3].

There are, however, patients who need a pharmacy preparation because there is no licensed alternative available on the market. To solve the conflict with the Dutch Medicines Act, PDPs have been authorised by the Dutch Health Care Inspectorate by means of a Circular Letter since 2007. [4] This Circular, which was brought to parliament by the Ministry of Health, Welfare and Sport, allows, under strict conditions, the preparation of unlicensed medicinal products in a preparing pharmacy and the distribution of these products to a dispensing pharmacy. The dispensing pharmacy can make an assessment concerning the pharmacotherapy, but the final responsibility about the preparation is with the preparing pharmacy. PDPs are only accepted in particular cases when there are no alternatives that have marketing authorisation available for the patient, so there is a danger that there is no adequate treatment. If there is a pharmacotherapeutic alternative for the pharmacy-made product, the PDP is not allowed to prepare or distribute the product.

The conditions for PDPs

PDPs are obliged to comply with the Circular's conditions that:

A. no licensed alternative medicinal product is available on the Dutch market;

B. the pharmacotherapeutic rationale is demonstrated;

C. product dossiers are available for all products;

D. production complies with Good Manufacturing Practice (GMP).

If the PDPs do not fulfill these conditions, they have to stop the preparation and distribution of these unlicensed products.

The general requirements of the Circular, background information concerning Dutch regulation and policies, selection of the PDPs, publication of inspection reports, and results of inspection visits related to the Circular's conditions "C" and "D" (product dossiers and GMP) are presented in a separate article[5]. The present article describes the compliance of Dutch PDPs with the requirement of the Circular that a special need must be shown for the pharmacy preparation.

Pharmacotherapeutic Alternatives (PA) and Pharmacotherapy (PT) investigation

PA and PT investigations are two requirements for PDPs that were introduced with the 2007 Circular:

1. PA investigation, where the pharmacist has to investigate and document the availability of licensed pharmacotherapeutic alternatives and has to show evidence that none of these alternatives are available before the pharmacist makes the pharmacy preparation.
2. PT investigation, where the pharmacist performs investigations on the pharmacotherapeutic rationale and has to show documented evidence for the need for the pharmacy preparation.

Objective of the article

The aim of this study is to assess the overall compliance of the PDPs with these two conditions, PA and PT investigations, of the Circular. Regular visits have been performed since 2007 by the Dutch Health Care Inspectorate to check the compliance of the PDPs with the Circular. PDPs not complying were revisited until they complied. If they did not comply during repeated visits, then they had to stop their preparation and distribution activities.

This article describes the results of the Dutch Health Care Inspectorate inspections carried out since 2007 for the PA and PT condition of the Circular, including such measures as enforcement.

PDPs are responsible for the documented evidence concerning the PA and PT investigations for all products.

2. Methods

The Inspectorate has developed an instrument to assess whether PDPs have carried out the PA and PT investigation adequately. Instructions were prepared by the associations of hospital and community pharmacists in order to teach PDPs how they could perform these investigations adequately. The interface between the pharmacists and the prescribers starts with the indication included in the PA/PT documentation. If there is uncertainty about a prescription or the indication, the pharmacist should contact the prescriber directly to clarify the matter.

Inspections aimed at judging the evidence-based PA and PT documentation

One of the aims of the inspections was to assess whether the PDP complied with the Circular's conditions for PA and PT. It needs to be demonstrated that the PDP is capable of performing and documenting the PA and PT investigations appropriately. In general, it was assessed whether the PDP had clear and unequivocal procedures on the one hand and whether the compliance with these procedures in daily practice was sufficient on the other hand.

To diminish inter-rater variability, assessments were carried out by inspectors who were trained and who were able to use table 1 where the scores from 1 to 4 are clearly defined.

Score for PA investigation at system level as assessed during PDP inspection

The assessment by the Inspectorate of the PA investigations carried out by the PDP consisted of three items to be scored. These are:

1. the procedure for assessing pharmacotherapeutic alternatives;
2. the criteria for the pharmacotherapeutic alternative included in the procedure;
3. the investigation of licensed pharmacotherapeutic alternatives based on a random check by the Inspectorate of the forms for selected products. This random check consisted of between three to five products.

The score for each of these three items could vary from 1-4, as it is shown in table 1

1 (absent)	The standard is absent; the standard is not followed and is not available in a documented form.
2 (available)	The standard is demonstrably available, but it is not followed consistently. The written procedures are available but not all employees involved in PA investigation are aware of the procedures.
3 (operational)	The standard is operational and is followed consistently. All employees working with the standard are aware of the written procedures but a regular evaluation or adjustment does not take place.
4 (guaranteed)	The standard is guaranteed and followed consistently. The employees are well aware of the written procedures. Moreover, regular evaluation takes place and, if needed, adjustment.

Based on observations and information gained during the visit to the PDP, the Inspectorate assessed each item to be scored as adequate if that item scored at least 3. A score of 4 is the level of quality to be strived for, but this score was not always assessed during the inspection visits.

The result for the Circular's condition relating to PA was considered to be sufficient if a score of at least 3 was given for each of the three above items to be scored. This means that the PDP has clear procedures and instructions on how to perform the PA investigation and that it follows these in daily practice.

Score for PT investigation at system level as assessed at the PDP inspection visit

The assessment by the Inspectorate of the PT investigations carried out in the PDP consisted of three items to be scored:

1. the procedure for assessing the pharmacotherapeutic rationale.
2. the assessment of the pharmacotherapeutic rationale for a stock preparation, based on a random check by the Inspectorate of the forms relating to a sample of selected products.
3. the minimum requirement for the level of evidence for prepared stock preparations distributed to other pharmacies.

PDPs use a classification scheme which ranges from A1 (a high level of evidence) to D8 (the lowest level of evidence) for assessing the pharmacotherapeutic rationale. This classification scheme is attached to this article as an appendix. [6] A1 refers to systematic reviews consisting of at least some investigations at an A2 level which consistently show evidence for the pharmacotherapeutic rationale. A2 refers to a randomised, double blind, controlled clinical trial of sufficient magnitude and consistency. D4 refers to evidence-based advice from national associations of specialists or national associations of pharmacists. D8 reflects a low level of evidence such

as where the pharmacotherapeutic treatment is only based on the individual insights of treating physicians without any objective clinical evidence.

For the distribution of stock preparations, the minimum requirement for the PDP is D4. This implies that there is an evidence-based, country-wide consensus for an application of the product for that particular indication.

The score for each of these three items could vary from 1 to 4, as shown in table 1.

The result for the Circular's condition relating to PT was considered sufficient if a score of at least 3 was given for each of the three items. This means that the PDP has clear procedures and instructions on how to perform the PT investigation and that it follows these.

3. Results

In 2007 and 2008, the Inspectorate selected the PDPs to be visited based on a questionnaire that was send to all pharmacies. A risk-based approach was applied in the sense that the PDPs with the highest number of dispensing pharmacies - that is clients- were visited first. The reason for this is that, in the case of a possible product defect, the consequences are greater if the product is distributed to more pharmacies. There was a large variation in the group of PDPs visited, but, for all PDPs, the number of dispensing pharmacies was at least 10. Nearly all PDPs that dispensed their products to at least 10 dispensing pharmacies have been inspected. The number of products per PDP varies from between five to ten, to up to hundreds of products. There are also large differences concerning the size of the batch and the quantities of the medicinal products distributed. However, changes in the status of the PDPs occur continuously, which means that the planning of the visits has to be adapted regularly. At present, there are still PDPs that decide to stop either their preparation or their distributing activities or both. The Inspectorate has performed repeated inspections at most of the PDPs that did not comply with the conditions of the Circular. PDPs that stopped distribution to dispensing pharmacies were visited to verify that they had, in fact, stopped.

3.1. Overall compliance of PDPs with the Circular's conditions at system level.

The results of the surveillance of the Inspectorate show that the compliance with the Circular's conditions has increased significantly and consistently since 2007. On November 1st, 2014 almost all PDPs distributing their product to more than 10 dispensing pharmacies had been visited by the Inspectorate. Of these, 18 complied and three nearly complied with the Circular's conditions while 10 had stopped distribution to dispensing pharmacies for various reasons. The progress made was possible because of the efforts of different stakeholders including the PDPs them-

selves, the associations of PDPs, and the Dutch Health Care inspectorate. A more detailed description of the overall compliance with the Circular's conditions can be found in a separate article[5].

3.1.1. Compliance of PDPs with the PA and PT conditions of the Circular at system level.

The PDPs are obliged to document the results of their PA and PT investigations for all products. By means of these PA and PT investigations, the pharmacist documents the added value of the unlicensed pharmacy preparation. The PDP uses primary criteria[7] such as efficacy, tolerability and safety, and secondary criteria[7] such as their experience with the product and how easy it is to use, in order to draw comparisons between the pharmacy preparation and the licensed alternative.

Examples are patients who are allergic to lactose or other ingredients of the registered product, or patients who need a lower dose than the registered dose of a medicinal product.

On November 1st, 2014, 20 out of the 21 PDPs visited had fulfilled the PA condition of the Circular at system level. Nineteen of the 21 PDPs had complied with the PT condition at system level. For these complying PDPs, the procedures for PA and PT are available and are followed consistently in daily practice. There were two PDPs that did not comply with the PA or PT condition. Their PA and PT documentation needed improvement.

The reports of the Inspectorate's visits to PDPs aimed to assess the quality assurance system the PDP had set up to comply with the conditions of the Circular. How the PDP's system functioned in daily practice was checked by the Inspectorate by means of a random check of the forms of selected products. If these forms were not available, or if they contained significant omissions, then the Inspectorate scored as insufficient the functioning of the PDP at system level.

3.2. Compliance of PDPs with the PA and PT conditions of the Circular at the level of the product.

We describe above how the Inspectorate assessed the compliance of PDPs with the conditions of the Circular at system level. This assessment by the inspectorate included a check on the functioning of the system in the PDPs in daily practice for a selection of products made during the visits.

Apart from the inspection aimed at assessing the quality assurance system for PA and PT, the inspectorate also requested in 2011 that all PDPs send a list containing the complete range of all products, including the actual numbers distributed per product. The product lists of all PDPs were reviewed and discussed by the Inspec-

torate in order to find 'clear' violations of the Circular's conditions. If the Inspectorate had concerns that those products might not fulfill the conditions of the Circular then the PDP was requested to send the PA and PT documentation. This request was based on a number of criteria. These were:

A. The number of units or packages distributed. Products with the highest numbers were selected preferably, as indicated in the list submitted by the PDPs.
B. Products which, in the opinion of the Inspectorate, were possibly obsolete or dangerous.
C. Availability of licensed alternatives on the Dutch market.
D. Combination products that raised questions to the inspectorate.

The Inspectorate received the PA and PT documentation of the products it selected from the PDPs. It then sent these to the National Institute for Public Health and the Environment (RIVM) to be assessed. The conclusions of the RIVM were discussed by the inspectorate with the PDP during the inspection visits. If, as in some cases, there was a clear pharmacotherapeutic rationale for the product, then the PA and PT documentation had to be improved. However, with other products, the PDP had to stop production and distribution altogether. If the PDP does not agree with the decision of the Inspectorate then the PDP can take legal steps in order to achieve a final judgement.

The results of the assessments of the RIVM are published in a report on the RIVM website[8].

3.2.1. Results of the PA and PT documentation of PDPs' products.

It is clear that PDPs had difficulty making accurate PA and PT documentation. The following deviations in the PA and PT documentation were found during the inspections:

- No comparison was made or documented with licensed pharmacotherapeutical alternatives.
- The comparison with other pharmacotherapeutical alternatives only consisted of products with the same compound.
- No comparison was made with other administration routes of the licensed alternatives.
- A ready to use (RTU) product was found with a higher dose than that recommended by the Formulary of Dutch Pharmacists (FNA) without justification or evidence offered for the higher dose recommended.
- The indication for the product was missing.

- The advantages of a combination product containing two licensed medicinal products over separate application of the two licensed products were not adequately documented.
- The pharmacotherapeutical rationale of thyroid powder of animal origin (thyreoideum) was not demonstrated while pharmacotherapeutical alternatives are available on the market.
- Evidence for the usefulness of the product for the indication was missing;
- The level of evidence for the pharmacotherapeutical rationale as assessed by the PDP was inadequate or missing;
- Documentation, including data from the literature, on the indication claimed for the product was not adequate to draw conclusions on its efficacy and safety.
- An unequivocal concentration for the product was missing.
- The starting material for the pharmacy preparation was not described in the product dossier.
- The advantage or added value of the product over the licensed alternative was inadequately documented in the product dossier;
- There was no proof that the D4 level, constituting a national consensus, was achieved.

Shortcomings were reported back to the PDP, with the request that they either take adequate measures to correct the shortcomings or stop distribution of the pharmacy preparation. Measures taken by the PDPs were checked during subsequent visits.

4. Discussion

Concerning the Circular's condition with regard to PA, the terms 'licensed pharmacotherapeutic equivalent' and 'licensed pharmacotherapeutic alternative' are used. Some PDPs focus on therapeutic equivalents and look for registered products with exactly the same active ingredient, the same dose and the same administration route. In recent years the views have changed in the sense that different compounds may be interchangeable as long as the indication is the same and the prescribing physician takes responsibility for the prescription.

The term 'therapeutic alternative', however, is difficult to define for the whole population. This is because what is an alternative for the majority of patients may not be an alternative for the minority who are insensitive or hypersensitive to that specific medicinal product. The pharmaceutical industry cannot always take into account the needs of smaller patient categories. A pharmacy preparation with another chemical substance for the same indication is sometimes unavoidable.

Sometimes the dose is a reason to opt for the pharmacy preparation, as the number of patients who need a lower or higher dose than the range of the registered alternative appears to be increasing. Thus, there is a need for more individualised therapy, which cannot always be covered through licensed medicinal products. Examples of patient categories where another dose may be needed are children and patients with impaired kidney function, including the elderly.

The criteria to be used for comparison with registered alternatives, as well as for the added value of the pharmacy preparation, are subdivided by the pharmacists into primary criteria and secondary criteria[7], suggesting that the weight of primary criteria for the individual patient is higher than that of the secondary criteria. Secondary criteria could be seen as soft criteria, but it is difficult to draw general conclusions for all patient categories. For example, 'ease of use' may be extremely important for patients with rheumatoid arthritis who may encounter difficulties in the handling of medicines, whereas this aspect may be of negligible importance for other patient categories.

There are PDPs that specialise in aseptic preparation and dispensing of parenteral medicines with a marketing authorisation which cannot be administered directly to patients - that is, they are not presented in ready-to-administer (RTA) form. For these medicines in particular, patient safety and medication safety are crucial topics in health care institutions[9]. The last steps in the process of individualising treatment with licensed medicinal products for patients sometimes need to be performed in a pharmacy or sometimes on the ward of a hospital. This may be done on the wards by employees who also have other tasks to perform and who do not always have a quiet environment in which to prepare the product or perform a complicated calculation. Therefore some hospital pharmacies and some PDPs offer the service of making so-called RTU (ready to use) and RTA[10] (ready to administer) products:

1. RTU is defined as an injection containing the active drug in solution at the required concentration and volume in a vial. The injection is then transferred to a final container, such as a syringe, infusion bag or elastomeric device, for administration to the patient.
2. RTA is defined as an injection containing the active drug in solution at the required concentration and volume, presented in the final container such as a syringe, infusion bag or elastomeric device, and is ready to be administered to the patient.

As a consequence of RTU and RTA the further processing of the product in the hospitals is simplified. This means a reduced number of preparatory steps in the process, a reduced need for calculations and no need for dilution. Reconstitution of parenteral medicinal products should preferably take place in a pharmacy assuming that the requirements concerning the safe preparation of sterile products can

be fulfilled. Pharmacy services such as RTU and RTA may reduce risks on the hospital wards and improve patient safety.

Some pharmacy preparations are based on development activities carried out by the Laboratory of Dutch Pharmacists (LNA) for the Formulary of Dutch Pharmacists (FNA). This means that the PDP can rely partly on LNA and FNA knowledge as long as the pharmacist can guarantee following exactly the procedure and processing proposed by the FNA, including having the correct equipment and expertise. Validation activities can simply be added to the already available FNA knowledge and can be simplified for FNA products.

Sometimes a pharmacy preparation is a second- or third- choice treatment. PDPs are only allowed to make these products if it can be shown that first- choice and/or second- choice treatments for this indication have failed or have given demonstrable adverse events. The pharmacist should be able to prove that the use of the product conforms to this treatment schedule.

During the inspections, the unlicensed product thyreoideum - one of animal origin - was encountered in one of the PDPs. The choice of this product was seen as irrational, because licensed pharmacotherapeutic alternatives are available on the market. There are risks associated with the use of thyreoideum concerning possible biological contamination and the application of the right dose. Incidents have been reported concerning its use. The preparation and distribution of thyreoideum to dispensing pharmacists is forbidden because this is not in accordance with the Circular's conditions. There may be a limited place for thyreoideum made on the basis of the magistral formula for patients who have shown a demonstrably unfavorable reaction to the registered alternatives. Privacy regulation including patient informed consent should be respected in any case.

Another case that the Inspectorate has encountered during the inspections was the topic of methotrexate syringes. The pharmaceutical company distributing the licensed methotrexate syringes enlarged the dose range of licensed syringes. When these additional syringes offering a new dose became available on the market, the preparation activities of some PDPs had to be stopped.

5. Conclusions

Almost all PDPs inspected complied with the PA and PT conditions of the Circular on a systematic level. The report of the RIVM[8], however, shows that the rationale of the pharmacy-made products is insufficient of insufficiently documented in a substantial proportion of the cases.

There is a national acceptance by hospital and community pharmacists, together with other important organisations in health care, to only make pharmacy prepa-

rations with a favourable pharmacotherapeutic rationale for which no licensed pharmacotherapeutic alternative is on the market.

PA and PT documentation of PDPs still requires attention. PA and PT documentation of a PDP should be available for all products and should show the added value for the patient.

Key Messages

What is already known on this subject

- The Medicines Act in the Netherlands is based on European Union (EU) Directive 2001/83/EC which forbids an unlicensed medicinal product being prepared and distributed by a preparing pharmacy (PDP= preparing and distributing pharmacy) to a dispensing pharmacy - that is one which dispenses the medicinal product to the patient.
- There are, however, patients that need a pharmacy preparation because there is no adequate licensed alternative medicinal product available on the market.
- Since 2007, the PDPs have been permitted by the Inspectorate by means of a so-called Circular. This Circular allows, under strict conditions, preparation of unlicensed medicinal products in a preparing pharmacy and distribution of these products to a dispensing pharmacy.
- The PDPs are only permitted if they fulfill the strict conditions of the Circular: absence of licensed pharmacotherapeutic alternatives; rational pharmacotherapy; compilation of a product dossier; compliance with GMP.

What this study adds

- The results of the inspection visits of the Dutch health Care Inspectorate show that almost all PDPs inspected complied with the PA and PT conditions of the Circular on a systematic level. The report of the RIVM[5] however shows that the rationality of the pharmacy-made products is insufficient of insufficiently documented in a substantial part of the cases.
- Some examples of medicinal products such as thyreoideum and methotrexate syringes and their place in pharmacotherapy are discussed.
- The Inspectorate is in consultation with the Ministry of Health, Welfare and Sport about how to proceed with the question of PDPs and the conditions they have to fulfill. Recent European case law concerning the interpretation of (EU) Directive 2001/83/EU will have to be taken into account.

Appendix: classification scheme showing the level of evidence for the pharmacotherapeutic rationale of pharmacy preparations.

Data in the literature concerning the criteria, efficacy, tolerability and safety, for a pharmacy preparation can be classified based on the level of evidence:

A1 Systematic reviews which comprise of, at least, some investigations carried out at A2-level, with results consistent with independent investigations.

A2 Randomised, comparative double blind controlled clinical trials of sufficient magnitude and consistency.

B Randomised clinical trials of poor quality or insufficient magnitude or other comparative trials such as, for example, non-randomised, comparative cohort investigations.

C Non-comparative investigation.

D Opinions of experts in the categories below varying from D1 to D8.

D1 Data from marketed products containing the same active medicine with a marketing authorisation in the Netherlands, the European Union, the United States, Canada or Japan.

D2 Published national consensus in the Netherlands such as 'Farmacotherapeutisch kompas, dermatica op recept, and the standards of the Dutch College of General Practitioners (NHG) and those of the institute CBO.

D3 Handbooks. Apart from pharmacotherapy handbooks there is a valuable handbook for pharmacy preparations in Germany entitled 'Neues Rezeptur Formularium'.

D4 The advice of national experts: Dutch associations of specialists or associations of pharmacists such as the working group for pharmacotherapy and pharmaceutical information of the Royal Dutch Pharmacy Association – 'De Werkgroep farmacotherapie en geneesmiddeleninformatie van de KNMP'.

D5 A verifiable decision of a group of professionals consisting of prescribers and pharmacists, where the process of decision-making is based upon a fixed procedure.

D6 The local advice of a hospital committee, such as the pharmaceutical committee or the formulary committee - 'de geneesmiddelencommissie' or 'formulariumcommissie'.

D7 The personal insights of individual prescribers and pharmacists with evidence consisting of objective, clinical data.

D8 The personal insights of individual prescribers and pharmacists without objective, clinical data.

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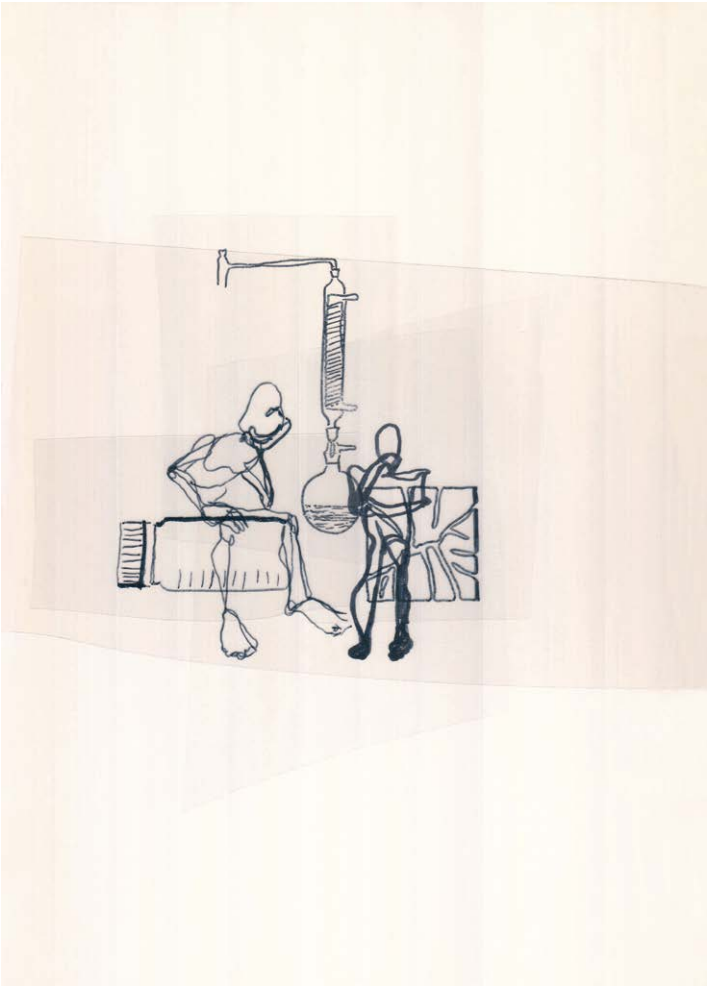


Chapter 8

General Discussion

General discussion

Medicinal products in health care

Medicinal products are essential for individual health care in Europe. Until approximately 1950, these medicinal products were in most cases prepared by pharmacists, either according to the magistral formula or the officinal formula[1]. Thereafter, there was a gradual shift in the preparation of medicinal products from the pharmacist towards the pharmaceutical industry[1]. Today, the large majority of medicinal products is prepared industrially, whereas pharmacy preparation remains important to cover the special medical needs of individual patients. Examples of special patient needs are the need for a product that does not cause an allergic reaction or the need for a product in an individually adjusted dose.

EU Regulation

Regulation of the preparation of medicinal products was started on a European level in 1965[2]. The regulation was set up after the Softenon tragedy in 1962[3]. The aim of the new regulation was to safeguard public health, while not hindering the development of the pharmaceutical industry.

The European Directive of 1965 was based on two important pillars:

- Product design quality
  The requirement of a marketing authorization was established. This means that a marketing authorization 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 should hold a manufacturing license issued by the competent authority. Compliance with Good Manufacturing Practices[4] is obliged for manufacturers of medicinal products.

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), irrespective of whether these products are made in a private company or in a pharmacy. Therefore, the regulation is mandatory for all persons and companies preparing IPMs.

Over the years many amendments have been made to European regulation. Since 1965, the requirements concerning the preparation of medicinal products have expanded. Today, the regulation of medicinal products is laid down mainly in Directive 2001/83/EC[5].

Exceptions to EU Regulation

In European Directive 2001/83/EU, some exceptions are described where the Regulation does not apply, such as specific pharmacy preparations and also medicinal products to fulfill special needs.

Pharmacists can legally prepare any medicinal product in the pharmacy by virtue of their professional education, professional license and the license of the pharmacy's premises. However, the exception for pharmacy preparations has to be interpreted very strictly and it relates only to the magistral formula and the officinal formula. The magistral formula is about pharmacy preparations that are prepared in accordance with a medical prescription for an individual patient. The officinal formula is a pharmacy preparation that is prepared in accordance with the prescriptions of a pharmacopoeia and which is intended to be supplied directly to the patients served by the pharmacy in question.

The reason for this exception in European Regulation is that medicinal products prepared in pharmacies are necessary to cover the special medical needs of individual patients that cannot be satisfied by IPMs.

Preparing and distributing pharmacies (PDPs)

Not every pharmacist in Europe prepares medicines today. One of the reasons that these so-called non-preparing pharmacies have emerged is that investments in quality and safety standards for preparation are not economically feasible for all pharmacies. Another reason is that the pharmacist may have changed his or her priorities within the profession in favour of the front-office activities, such as pharmaceutical care where consultation with other health care professionals is crucial, instead of the traditional back-office work, which includes pharmacy preparations.

These non-preparing pharmacies are dependent on PDPs for special medicinal products. These PDPs prepare medicinal products in their pharmacy and distribute these products to a non-preparing dispensing pharmacy. Some of these PDPs have developed into companies that prepare medicinal products on a large scale, while retaining their formal status as a pharmacy.

Questions over the legal position of PDPs

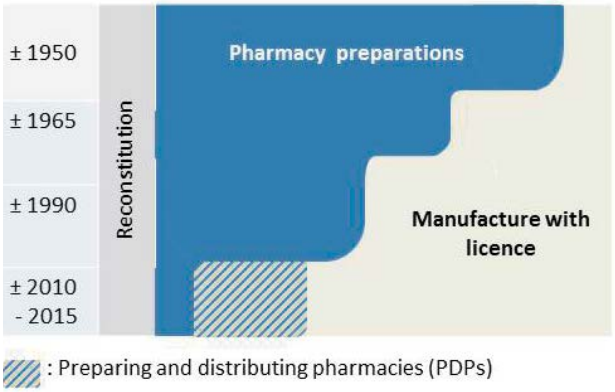
There is a dilemma between the European regulation and its two pillars aiming at safeguarding public health on the one hand and the medical need for medicinal products in individual health care on the other hand. Many pharmacies in Europe cannot themselves prepare medicinal products on the basis of the magistral and

officinal formulae for their patients and so are dependent on PDPs for these medicinal products. However, although these PDPs are, legally, pharmacies, they are acting as pharmaceutical companies. The question is therefore: can PDPs use their formal legal status as a pharmacy in order to prevent the strict requirements of the Directive 2001/83 being applied?

European regulation has expanded enormously since 1965, leaving fewer legal opportunities for pharmacy preparations and individual health care. This is illustrated in figure 1:

Figure 1

Legal and pharmaceutical developments in time in the production of medicinal products



The grey section in Figure 1 corresponds to manufacturing in the pharmaceutical industry, whereas the blue section refers to pharmacy preparations. The area with blue / grey stripes refers to pharmacy preparations of PDPs. PDPs are pharmacies that do not fit into the 'old' concept of pharmacy preparation, therefore they are placed outside of the blue area. PDPs prepare medicinal products for other pharmacies, on a larger scale than that which is usual in pharmacies.

Recent case law is presented in chapter 4. This case law confirmed that the legal opportunities for pharmacy preparations are very limited. The European Court of Justice (ECJ) provided a strict interpretation of the exceptions stated in Article 3 of Directive 2001/83/EC. For the magistral formulae the medicinal product should be prepared in accordance with a medical prescription that needs to be issued in advance by a physician for a specific patient. It should be issued before the medicinal product is prepared for that patient. For the officinal formulae, the medicinal product is prepared in a pharmacy and supplied directly to the patients served by this pharmacy.

Consequently, the exception for pharmacy preparations does not allow pharmacies to prepare on a large scale and to distribute magistral formulae or officinal formulae to other pharmacies. Although they are not addressed in current European

regulation, PDPs do not fall under its exceptions based on recent case law. PDPs have to comply with European regulations and the exceptions for pharmacy preparations do not apply to them.

Many European states have attempted to find national solutions for these PDPs in order to permit individual health care where it is needed and to ensure that medicinal products are safe, effective and of high quality. Examples of national solutions are the Circular letter in the Netherlands[6] and the 'specials' licence in the UK[7].

Two studies performed in the Netherlands, presented in chapter 6 and 7, showed that the Circular is well accepted and followed by the PDPs. This means that pharmacy preparations are only prepared if there is a favourable pharmacotherapeutic rationale and if no licensed pharmacotherapeutical alternative is on the market. In addition, a product dossier should be available for all products to ensure the product design quality and production quality comply with Good Manufacturing Practice (GMP).

The question is whether, given the current EU legislation, these attempts at national solutions are tenable in the long term.

Recent case law, described in Chapter 4 emphasises that economic factors cannot be used to affect European regulation, in particular Directive 2001/83/EU. We can conclude from the case of the European Commission versus the Republic of Poland that a marketing authorisation of an EU member state is required, even if cheaper licensed medicinal products, with the same ingredient, the same concentration and the same dosage form, could be imported from other member states. The member states have other options for addressing economic factors, for example by the setting of prices for the medicinal products or through the inclusion of products in national health insurance schemes.

A new development in the Netherlands is the introduction of a national inventory, the so-called G-standard, of unlicensed medicinal products prepared and distributed by the PDPs. We have seen in Chapter 3 that an inventory for pharmacy preparations was included in the quality and safety standards of 2011. This national inventory is publically available and gives an overview of the products of the different PDPs. Since 2016, it is mandatory for Dutch PDPs to include their products in the national inventory. With the inclusion in the national inventory, the products of PDPs are now part of the software programmes available to pharmacies in order to perform medication surveillance for individual patients. This marks a significant increase in medication safety. These products are evaluated on a regular basis with regard to their inclusion in national health insurance schemes. In the Netherlands, the Circular Letter determines whether there is a rationale for the product. We have seen this in Chapters 6 and 7. If there is no rationale for the product, then the product should not be prepared and dispensed by the PDPs. The considerations for

including, or not, these products in the insurance systems are outside the scope of this thesis.

Quality and safety standards for pharmacy preparations

For the limited legal opportunities left for pharmacy preparations, which corresponds to the blue area in Figure 1, the quality and safety standards are determined by individual European states. European regulation does not apply to these pharmacy preparations.

The Committee of Experts on Quality and Safety Standards in Pharmaceutical Practices and Pharmaceutical Care (CD-P-PH/PC) at the Council of Europe, hereafter, the Committee of Experts, supported by the European Directorate for the Quality of Medicines & Healthcare (EDQM), has worked on the harmonization of the quality and safety standards for pharmacy preparations in the different member states.

In Chapter 2, a study on quality and safety standards, organized among European countries in 2008, is described. The study highlighted several factors:

- Pharmacy preparations
  It showed that there is a gap in the quality and safety standards for industrial manufacture and pharmacy preparation respectively. The main differences were related to the product design quality and the production quality.
- Medicinal products made in the clinical areas of health care establishments.
  It also showed that there is a gap between medicinal products prepared in pharmacies and in clinical areas, respectively. In most countries, there are no or few quality and safety requirements defined for preparations in clinical areas.

The results of this study showed a lot of variation in the quality and safety standards that are applied in Europe. This was particularly true for the requirements for quality in production. The study also showed that, in general, requirements for product design quality are missing. Moreover, the study showed that there are different standards for PDPs.

The results of this study were discussed at an invitational workshop in 2009 with experts from health authorities and from the field of pharmaceutical practice. Thereafter the Committee of Experts elaborated the proposals further and prepared a draft resolution text, which was submitted to the Committee of Ministers by the end of 2010.

Resolution CM/ResAP(2011)1 on quality and safety assurance requirements for medicinal products prepared in pharmacies for the special needs of patients was adopted by the Committee of Ministers of the Council of Europe on 19 January 2011[8].

A study that was set up in 2013/2014 to assess the impact of the adopted Resolution is described in Chapter 3. This study showed that with regard to production quality, GMP is required in most of the countries for high-risk pharmacy preparations. For PDPs, for example, the GMP requirement and the requirement to comply with good distribution practices (GDP) is followed in most of the countries. The study also showed that concerning the product design quality, some countries have included the need for a product dossier in their regulation, whereas some other countries have planned to include this requirement in their regulation. These main findings are in accordance with the recommendations of the Resolution. In general, this study showed that there is a clear commitment to implement the recommendations of the Resolution.

The requirements for the quality and safety assurance of medicinal products for patients with special needs are described in Chapter 3. These focus on specific structures and specific processes related to pharmacy preparation. The new aspects presented in Chapter 3 are needed to ensure patient safety and the added value for the patient in Europe. This is in addition to the existing product specific requirements in the Pharmacopoeia. The chapters and monographs of the European Pharmacopoeia contain general and specific requirements applicable to medicinal products prepared in pharmacies. The European Pharmacopoeia describes, in particular, the standards and methods for the control of the chemical, pharmaceutical and microbiological quality of active substances and excipients, and for the control of dosage forms and containers. The new requirements refer to the European Pharmacopoeia or, in its absence, to a national pharmacopeia. The implementation of these new quality and safety standards is studied in Chapter 3. Indeed, one of the conclusions of this study is that member states do comply with the legally binding requirements of the pharmacopoeia.

However, this study also showed that there is still room for improvement in some areas. For example, there is little implementation of the recommendation of the Resolution that the competent drug regulatory authorities should consider establishing the requirement to obtain a marketing authorization, including full compliance with GMP, for specific pharmacy preparations and in specific cases. It would be in the interest of the patient to work further on the implementation of this recommendation.

There were also interesting findings concerning the recommendation that pharmacy preparations are not advisable if a suitable pharmaceutical equivalent, with a marketing authorization, is available. This study showed that for PDPs in some countries a more severe requirement than this recommendation is put into place. In these countries, it is not allowed to prepare and distribute a medicinal product to other pharmacies if a licensed pharmacotherapeutic alternative is available on the market.

Quality and safety standards for reconstitution practices in health care establishments for medicinal products for parenteral use

The study described in Chapter 2 highlighted that few or no quality and safety requirements were defined for preparations in clinical areas in health care establishments[9].

The study discussed in Chapter 5 showed that high risks for patients are associated with the reconstitution of parenteral medicines. In European health care 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 harm to patients. This is, in particular, the case in health care establishments where these aseptic preparations are carried out in hospital pharmacies as well as in clinical areas. In these different locations, pharmacies and clinical areas in the health care establishment, the risk profile may be different, depending on the conditions that exist in the location such as, for example, the premises, the personnel and the equipment[10].

This study offered some options to improve the process for aseptic preparations in health care establishments for the benefit of the patient. These options include, for example, the nomination of a designated person in the health care establishment, with appropriate qualifications, to take overall responsibility for the reconstitution process of parenteral medicines. An overview can be made with the help of this designated person of the various reconstitution activities for the different locations within the health care establishment, such as the pharmacy and the clinical areas. This would then distinguish the different risks. With the help of this information, a risk assessment for the whole health care establishment can be performed. This risk assessment can serve as a basis for a decision by the board of directors about where the reconstitution activities can be performed safely.

After discussing the results of this study, the Committee of Experts elaborated the proposals further and prepared a draft resolution text, which was submitted to the Committee of Ministers in May 2016. Resolution CM/Res(2016)2 on good reconstitution practices in health care establishments for medicinal products for parenteral use was adopted by the Committee of Ministers on 1 June 2016[11].

Further studies are needed to investigate the measures taken on the level of individual member states in order to follow the recommendations of this recently adopted Resolution.

Conclusions and implications

The harmonised quality and safety standards on pharmacy preparations[8] are aimed at protecting patient safety and in preventing gaps in the quality and safety between medicinal products prepared in pharmacies and those made in industrial settings. The fact that these standards are available is a breakthrough for the patient. The patient is entitled to a product of good quality that fulfills these quality and safety standards.

However, there is another problem as there are now fewer legal opportunities for pharmacy preparations. In the interest of the patient a reform of European regulation of the preparation of medicinal products is recommended. The legal opportunities for pharmacy preparation have diminished over the years. PDPs have taken over a large part of the magistral and official formulae of non-preparing dispensing pharmacies. However, although not addressed in current European regulation, PDPs do not fall under the exceptions of the magistral and officinal formula in European regulation. This is shown in a study in Chapter 4 where recent case law is presented. A return to the old situation where every pharmacy prepared medicinal products according to magistral and officinal formula is probably not a realistic option and not in the interest of the patient. These non-preparing pharmacies have lost the expertise, facilities and equipment to prepare medicinal products that are safe, effective and of high quality.

Medicines supplied by the pharmaceutical industry are essential in the treatment of millions of patients in Europe every day. However, over the last few years shortages in the supply of these medicines have become increasingly common and may be a threat for individual health care. It is in the interest of society that medicines can be prepared in PDPs or companies, for example in the case of shortages of licensed medicinal products. In some cases, these shortages can be met by importing a licensed alternative from another European country. In other cases, a PDP could make a similar product. It is permitted, in the Netherlands, for a PDP, under the conditions of the Circular Letter, to make medicinal products for which no licensed therapeutic alternative is available on the market. This supply through a PDP is, however, only temporary and should not be taken as justification for long-term supply. Supply of the medicinal product through the PDP should cease as soon as it is practicable following the re-instatement of the licensed product. Economic factors can play an important role for pharmaceutical companies as well as for PDPs. However, no specific provisions are included in the Medicines Act concerning the supply of medicines by means of a pharmacy preparation when shortages occur. Further research is needed in this important area to guarantee the continuous supply of medicines for the patient.

Many European countries are attempting to provide national solutions for PDPs to permit individual health care where it is needed, and to ensure that medicinal

products are safe, effective and of high quality. These could serve as input for the recommended reform in European regulation. Further study is needed to investigate whether these different national solutions are legally justified.

An important pillar of European regulation concerning the quality of medicinal products is the requirement of a marketing authorisation as described in Chapter 4. This requirement is obligatory for all medicinal products prepared industrially or manufactured by a method involving an industrial process (IPMs). This is irrespective of whether these products are made in a pharmaceutical company or in a pharmacy. The application for a marketing authorisation for a medicinal product requires, in general, considerable investments. These investments are economically feasible for products manufactured on an industrial scale, which are aimed at serving the needs of the majority of the patients. However, in general, these investments are not economically feasible for medicinal products made in pharmacies, for which no licensed therapeutic alternative is available on the market. However, if a PDP makes medicinal products in larger quantities for the special needs of patients, then a license for that medicinal product would be appropriate, because the requirements for the industry, and for pharmacies, are the same, as explained in Chapter 4. Included in the new quality and safety standards, adopted in 2011, is the requirement that competent drug regulatory authorities should consider how to deal with the product design quality and how to establish criteria for a marketing authorisation, if applicable, for pharmacy preparations. Economic factors can be taken into account, where appropriate, because considerable investments may be needed for obtaining a marketing authorisation for pharmacy preparations. More research is needed in this area to develop these criteria for a marketing authorisation.

The resolution for pharmacy preparation offers an opportunity to pharmacists and authorities to improve the quality of their work and to prevent patients suffering harmful incidents. A study, described in Chapter 3, has shown that in the member states much progress has already been made in the implementation of the quality and safety standards mentioned in the Resolution. However, the further implementation of the Resolution, in particular as far as PDPs are concerned, is hampered by the limited legal opportunities left for pharmacy preparations in European regulation. This is not in the interest of the patient.

From the Chapters 2 and 5, we can conclude that there is little or no regulation in most of the member states regarding the reconstitution of parenteral medicines in healthcare establishments. The resolution on good reconstitution practices, adopted on June 1st, 2016 fills this gap. This standard on good reconstitution practices is a major step in the improvement of patient safety and it offers a challenge for further improvement by reducing the risks associated with the reconstitution of parenteral medicines. Further studies are needed to show how the implementation of these good reconstitution practices develops over time in the different member states.

Considerations for the future

It is clear that positive developments have taken place in pharmacy preparation in recent years. However, the problem we face is that European regulation, more specifically Directive 2001/83/EC, is outdated. European regulation was created at a time when every pharmacist made medicinal products for his or her own patients and when large-scale pharmacy preparation did not exist. Nowadays, many pharmacies have stopped preparing products and have outsourced preparation to PDPs.

Since 2011, there are harmonised quality and safety standards in Europe based on a consensus among the 37 member states of the Council of Europe. These are the states parties to the convention on a European Pharmacopoeia. These standards are crucial for the safety and quality of individual healthcare. This consensus shows that the political will exists in these European countries to create adequate quality and safety standards for pharmacies, including PDPs, to serve the special needs of patients.

Pharmaceutical companies, as well as pharmacies, are involved in individual healthcare; but pharmacists are confronted with the special needs of patients for which no licensed industrial product is available on the market. These special needs have to be taken care of by pharmacists. Society expects the pharmacist to dispense a pharmacy preparation dedicated to the special needs of patients. For example a product that does not cause an allergic reaction or the need for a product in an individually adjusted dose. Indeed, this is often the case for children or the elderly.

In Chapter 4, we have discussed the interpretation of the European Court of Justice in the Abcur case in 2015, which has caused a lot of uncertainty among pharmacists in Europe. This uncertainty is based upon concerns that there might no longer be a legal place for PDPs making preparations on a larger scale – that is aimed at serving the special medical needs of patients. Until now this uncertainty has not been taken away, although some European countries have taken different actions in order to protect the care of patients with special needs.

As discussed in Chapter 3, many different 'solutions' have been implemented in European countries to guarantee the care of patients with special needs. It has been shown that the national authorities of these European countries have taken steps to improve their national standards for pharmacy preparation by implementing the new European standards of 2011.

From among these different national 'solutions' that are available in Europe, the Dutch situation is presented in Chapters 6 and 7. The Dutch studies showed that the PDPs complied with the quality and safety standards, introduced in 2007 through the Circular Letter and which described the qualitative conditions that

must be fulfilled by the PDPs. This Circular Letter was needed in order not to obstruct patient care, because the Dutch Medicines Act is based on Directive 2001/83/EC which forbids a PDP from preparing and distributing unlicensed medicinal products to dispensing pharmacies. Based on the experiences since 2007, the Circular describing the enforcement strategy of the Inspectorate, was extended in August 2016. This was supported by the relevant stakeholders both in and outside of the Dutch Ministry of Health, Welfare and Sport. New modules were included in the new Circular Letter in addition to the already existing quality modules, such as the GMP requirement and the absence of licensed pharmacotherapeutic alternatives. These new modules included pharmacovigilance and the requirement to include the products of PDPs in a national inventory. These were aimed at improving, further, the already existing quality and safety standards.

The harmonised quality and safety standards of 2011, and the quality modules of the different national 'solutions', could serve as a basis for a necessary change in European regulation. This is needed urgently from the perspective of the patient. Since the Abcur case in 2015, there are however no signs that European lawmakers have taken initiatives to adapt European regulation to the direction where European countries have already gone more than a decade ago. It is of crucial importance for the patient with special medical needs that the role of pharmacists in individualised healthcare is strengthened. This role should be based upon up-to-date European regulation, built on the existing pillars regarding the quality of product design and production and which refers to adequate quality and safety standards for pharmacies and PDPs.

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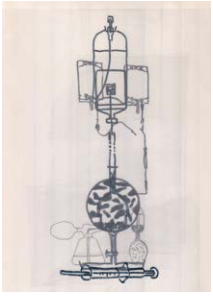


Valorisation

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.

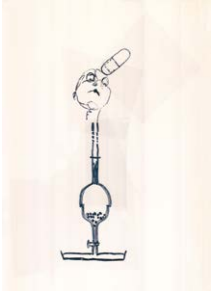
The implications for further research in the area of pharmacy preparation are also included in this thesis. This research should be aimed at making the best use of the harmonised quality and safety standards and the different national solutions for

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



Summary

Individualised health care

Both in Europe and elsewhere in the world, medicinal products are essential for offering individual health care to treat patients for their medical conditions. These medicinal products can be made by a pharmaceutical company or in a pharmacy. What counts for the patient is that the quality of the product is guaranteed, irrespective of where the product is made. Medicinal products should be safe, effective and of high quality. Medicinal products of poor quality can have serious consequences for patients.

Pharmacy preparation

The majority of medicinal products today are made by a pharmaceutical company. The preparation of medicinal products in pharmacies remains, however, of crucial importance. Products prepared in a pharmacy are essential for patients with special medical needs. In today's society, we expect the pharmacist to dispense a pharmacy preparation that is dedicated to the special needs of the patient. This, for example could mean, a product which does not cause an allergic reaction or one which must be dispensed in an individually adjusted dose. This is often the case for children or the elderly.

The European regulation

Regulation for medicinal products was established on a European level through Directive 65/65/EC in 1965, following the notorious Softenon tragedy three years earlier. The European regulation applies to all medicinal products prepared industrially or manufactured by a method involving an industrial process, irrespective of whether these products are made by a company or in a pharmacy. The main pillars upon which this European regulation has been built are the product design quality and the production quality.

The product design quality is documented in a registration dossier which contains technical data, administrative data and non-clinical and clinical data about the medicinal product. Each medicinal product must obtain a marketing authorisation based on this registration dossier and issued by the competent authority before the product is placed on the market.

The production quality is ensured by the requirement that the producer must hold a manufacturing licence issued by the competent authority. The manufacturing licence is dependent upon compliance with Good Manufacturing Practice (hereafter: GMP).

Exceptions to the European regulation

Some exceptions are described in the European regulation, in particular Directive 2001/83/EC, where the regulation does not apply. These cover specific, small-scale, pharmacy preparations and also medicinal products which fulfil special needs. It is legal for pharmacists to prepare any medicinal product in the pharmacy by virtue of their professional education, professional licence and the authorisation of the pharmacy's premises. These exceptions to the European regulation are created because they are needed for the treatment of patients with special medical needs.

A systematic review was carried out in some European member states of the Council of Europe in order to study the general quality and safety standards for pharmacy preparations. This review included legal provisions and definitions, the practices and provisions for the preparation and delivery between pharmacies and the product quality. This study, described in **Chapter 2**, showed that there is a gap in the quality and safety standards between preparation in pharmacies and the manufacture at the industrial level. The study also showed that there is a gap in the quality and safety standards between medicinal products prepared in pharmacies and those prepared on hospital wards. Indeed, in most of the countries there is little or no regulation laid down for preparations on hospital wards. Moreover, the study showed that in most of the countries there are Preparing and Distributing Pharmacies (hereafter: PDPs) which, distribute medicinal products to a dispensing pharmacy, that receives the prescription for a patient, and provides the pharmacy preparation, made by the PDP, to the patient.

Guidelines had been proposed for the quality and safety standards for medicines prepared in pharmacies and this has led to the adoption of the Resolution on pharmacy preparations by the Committee of Ministers of the Council of Europe on 19 January 2011. The quality and safety parameters in this Resolution comprised many different aspects of pharmacy preparations. These included: the benefits of the pharmacy preparation for the patient; the quality standards for preparation and distribution; marketing authorisation; the need for product dossiers to document the quality of the product's design; and reporting safety issues to the national authorities. A method for risk assessment is applied in the Resolution in order to discriminate between low-risk and high-risk pharmacy preparations and to adjust the level of the quality and safety standard to the risk level. One of the recommendations of this Resolution is that the Good Manufacturing Practice (GMP) quality system should be used for "high-risk preparations".

European countries were requested to implement this Resolution, while taking into account their national frameworks.

Another systematic review was performed in some European member states of the Council of Europe in order to study the implementation of the Resolution. This is described in **Chapter 3**. This study has shown that European countries have made good progress and have a clear commitment to implement the recommendations of the Resolution.

This study also mentioned that medicinal products are regulated in the EU by Directive 2001/83/EC and Regulation (EC) No 726/2004. This EU legislation offers opportunities for pharmacy preparations, but only under certain strict conditions as defined in these regulations. PDPs do not always fulfil these strict conditions.

A study into the legislation covering the preparation of medicinal products in European pharmacies, presented in **Chapter 4**, shows that there are two pillars which only apply in cases where the Directive 2001/83/EC itself is applicable. The Directive applies to any medicinal product that is prepared industrially or manufactured by a method involving an industrial process as determined by Article 2 (1) of Directive 2001/83/EC. This includes the marketing authorisation of the medicinal product and the authorisation of the manufacturer for manufacturing. Products that do not fulfil the conditions of Article 2 are not subject to the provisions of the Directive.

This study also showed that the recent interpretation of the European Court of Justice (ECJ) concerning the scope of EU Regulation limits the opportunity for pharmacy preparations. The ECJ provided a strict interpretation of the exceptions to the Directive 2001/83/EC stated in Article 3. For the magistral formulae, the medicinal product should be prepared in accordance with a medical prescription which needs to be issued by a doctor for a specific patient in advance - that is before the medicinal product is prepared for that patient. For the officinal formulae, the medicinal product must be supplied directly by the pharmacy which prepared it to the patients supplied by that same pharmacy. Consequently, the exception for pharmacy preparation is not applicable to pharmacies that prepare on a large scale and who distribute officinal formulae or magistral formulae to other pharmacies. PDPs are not addressed in the current European Regulation, but, based on the ECJ decision, they have to comply with this regulation because the exceptions for pharmacy preparations are not applicable to them.

The study does not show whether the exception of Article 5 of Directive 2001/83/EU could offer opportunities for PDPs. Further studies are needed to investigate this.

In many different European states of the Council of Europe, there are attempts at national solutions to allow these PDPs to permit individual health care where it is needed and to ensure that medicinal products are safe, effective and of a high quality. Examples of attempts at national solutions are the Circular letter in the Netherlands and the 'specials' licence in the United Kingdom.

The observational studies which were performed in the Netherlands, presented in **Chapter 6 and 7**, show that the Medicines Act is based on European Union (EU) Directive 2001/83/EC. The Medicines Act forbids a PDP from preparing and distributing unlicenced medicinal products to dispensing pharmacies. In order not to obstruct patient care, the Dutch Inspectorate has sent a Circular Letter to all Dutch pharmacists. This circular states the conditions which must be fulfilled by the PDPs. If PDPs had not been complying with these conditions during repeated visits, they were forced to stop their preparation and distribution activities. The conditions of the Circular Letter are: An absence of licenced pharmacotherapeutic alternatives, rational pharmacotherapy, a product dossier for all products, and compliance with GMP. These studies show that the Dutch Circular is generally accepted and followed.

Another area where patient safety is important is the aseptic preparation of parenteral medicinal products in health care establishments. Errors in the preparation of these medicines may lead to a product that can cause immediate harm to patients. In **Chapter 5,** we present the risks associated with these aseptic preparation processes and the consequences of poor reconstitution practices.

Aseptic preparation is carried out in hospital pharmacies as well as in clinical areas in health care establishments. In many cases parenteral medicines with a marketing authorisation cannot be administered directly to patients, which means that they are not presented in a form which is ready to administer. 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 a routine pharmacy preparation.

The observational study presented in **Chapter 2**, demonstrated that there is none or very limited regulation concerning reconstitution in Europe. The risks associated with the preparation of these medicines, and options for good reconstitution practices, were studied in **Chapter 5**.

Guidelines have been proposed for good reconstitution practices in health care establishments for medicinal products for parenteral use. This has led to the adoption of the Resolution on 'good reconstitution practices (GRP) in health care establishments for medicinal products for parenteral use'. This, was adopted by the Committee of Ministers on 1 June 2016.

The quality and safety parameters in this Resolution comprised many different aspects of reconstitution. These included, for example, the responsibilities of the authorities and the responsibilities of the health care establishment. This may include the management, the designated person and the personnel in clinical areas. Moreover, a risk assessment approach was presented that can be of help to the management of the health care establishment in deciding where the products can best be reconstituted, such as in the pharmacy or in the clinical area. Moreover,

minimum requirements or standards for reconstitution in clinical areas were presented. This includes, for example, an overall procedure for reconstitution for the health care establishment, the availability of detailed technical instructions for all products, the competency of the personnel required and an approved list of products per clinical area which can be reconstituted. Further studies are needed to study the impact of this Resolution on good reconstitution practices in the different European countries.

A change in the European Regulation, more specifically in Directive 2001/83/EU, covering pharmacy preparation is both necessary and urgent from the perspective of the patient. The European Regulation is outdated. It has been created in a time when every pharmacist made medicinal products for his or her own patients and when large scale pharmacy preparation did not exist. Today, many pharmacies have stopped preparing products and have outsourced their preparations to PDPs.

The harmonised quality and safety standards of 2011, discussed in **Chapter 3**, and the quality modules of the different attempts at national solutions, such as those presented in **Chapters 6 and 7**, could serve as a basis for this necessary change in the European Regulation - that is one built upon the two pillars of product design quality and production quality which already exist.

We presented the implications for further research. A structured approach for future research in the area of pharmacy preparations in Europe is advisable in order to coordinate all the efforts aimed at serving the interests of the patient.

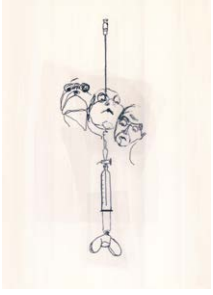
Research is needed on how to make use of the harmonised quality and safety standards of 2011 and the quality modules of the different attempts at national solutions in a way that they can serve as a basis for a necessary change in the European Regulation. One example of such a study would be to investigate the conditions concerning the requirement, applied in some countries, that pharmacy preparations are not allowed if a suitable pharmaceutical equivalent, with a marketing authorisation, is available. Moreover, in order to serve the patient better, further research is needed in order to investigate whether the different attempts at national solutions can fit into a legal framework.

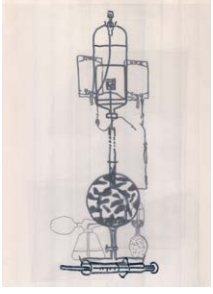
Research is needed to assess which pharmacy preparations under which conditions should be considered by the competent drug regulatory authorities for whether they require marketing authorisation. Research is also needed concerning the requirement for PDPs to comply with the GMP for production quality and to investigate whether the exception of Article 5 of Directive 2001/83/EU could offer opportunities for PDPs.

The important area of drug shortages should also be studied in order to assess if, and under which conditions, pharmacy preparations could play a role in prevent-

ing them and, whether this is in the interest of the patient and what could then be the legal basis for such action.

It would also be very worthwhile for patient safety, if further research was conducted on the impact of the recently adopted quality and safety standards for good reconstitution practices in the different European countries.





Samenvatting

Individuele gezondheidszorg

In Europa en elders in de wereld zijn geneesmiddelen essentieel voor individuele gezondheidszorg teneinde patiënten te behandelen voor hun aandoeningen. Productie van deze geneesmiddelen kan plaatsvinden in een farmaceutische bedrijf of in een apotheek. Wat telt voor de patiënt is dat de kwaliteit van het product gegarandeerd is, onafhankelijk van de plaats waar het product gemaakt is. Geneesmiddelen moeten veilig, effectief en van hoge kwaliteit zijn. Lage kwaliteit van geneesmiddelen kan ernstige gevolgen hebben voor patiënten.

Apotheekbereiding

Heden ten dage worden de meeste geneesmiddelen geproduceerd door de farmaceutische industrie. De bereiding van geneesmiddelen in de apotheek blijft echter van cruciaal belang. In de apotheek bereide geneesmiddelen, c.q. apotheekbereidingen, zijn onmisbaar voor de patiënt met speciale medische behoeften. De maatschappij verwacht van de apotheker dat hij of zij een product ter hand stelt gericht op de speciale behoeften van patiënten, zoals bijvoorbeeld een product dat geen allergische reactie veroorzaakt of een product in een individueel bepaalde dosis bijvoorbeeld voor kinderen of ouderen.

Europese wet- en regelgeving

Wet- en regelgeving voor geneesmiddelen is op Europees niveau opgezet in Richtlijn 65/65/EC in 1965, na de wel bekende Softenon tragedie in 1962. Europese wet- en regelgeving geldt voor alle geneesmiddelen die industrieel zijn bereid of zijn geproduceerd met een methode gebaseerd op een industrieel proces, onafhankelijk van de vraag of deze geneesmiddelen in een farmaceutisch bedrijf of in een apotheek zijn gemaakt. De pijlers waarop de Europese wet- en regelgeving is gebaseerd zijn de productontwerpkwaliteit en de productiekwaliteit.

De productontwerpkwaliteit wordt gedocumenteerd in het registratie dossier, dat technische - en administratieve gegevens bevat evenals niet-klinische en klinische data inzake het geneesmiddel. Gebaseerd op dit registratiedossier, wordt voor ieder geneesmiddel een handelsvergunning afgegeven door de Europese Gemeenschap of het College ter Beoordeling van Geneesmiddelen voordat het geneesmiddel in het handelsverkeer wordt gebracht.

De productiekwaliteit wordt geborgd door het feit dat de producent een fabrikantenvergunning dient te hebben, die is afgegeven door de bevoegde autoriteit. De fabrikantenvergunning is afhankelijk van het voldoen aan de eisen inzake Goede Manieren van Produceren (hierna: GMP).

Uitzonderingen op Europese wet- en regelgeving

In de Europese wet- en regelgeving, in het bijzonder Richtlijn 2001/83/EC, worden enkele uitzonderingen beschreven waar deze niet van toepassing is, zoals specifieke kleinschalige apotheekbereidingen en ook geneesmiddelen die gericht zijn op de speciale medische behoeften van de patiënt. Apothekers mogen wettelijk elk geneesmiddel bereiden in hun apotheek op basis van hun professionele educatie, hun professionele apotheekinschrijving en de autorisatie van de apotheekgebouwen. Deze uitzonderingen in Europese wet- en regelgeving zijn gecreëerd omdat ze nodig zijn voor de behandeling van patiënten met speciale medische behoeften.

Er is een systematische review uitgevoerd in enkele Europese landen behorende bij de Raad van Europa teneinde de algemene kwaliteits- en veiligheidsstandaarden voor apotheekbereidingen te bestuderen, alsmede de wettelijke voorzieningen en definities, de praktijken voor bereiding en aflevering tussen apotheken en de productkwaliteit. Deze studie is beschreven in **hoofdstuk 2** en laat zien dat er een 'gap' is in kwaliteits- en veiligheidstandaarden voor respectievelijk apotheken en productie op industrieel niveau. De studie laat tevens zien dat er een 'gap' is in kwaliteits- en veiligheidstandaarden voor geneesmiddelen die zijn bereid in respectievelijk apotheken en afdelingen van gezondheidszorginstellingen en dat er in de meeste landen geen of weinig wet- en regelgeving is voor bereidingen in ziekenhuisafdelingen. Voorts liet de studie zien dat er in de meeste landen bereidende en collegiaal leverende apotheken (hierna: BCLA's) zijn, die geneesmiddelen distribueren aan andere apotheken, die het recept van de patiënt ontvangen en de apotheekbereiding, die door de BCLA is gemaakt, ter hand stellen aan de patiënt.

Richtlijnen zijn voorgesteld voor kwaliteits- en veiligheidsstandaarden voor geneesmiddelen die in de apotheek zijn bereid en dit heeft geresulteerd in het aannemen van de Resolutie apotheekbereidingen door het Comité van Ministers van de Raad van Europa op 19 januari 2011. De kwaliteits- en veiligheidstandaarden in deze Resolutie omvatten veel verschillende aspecten van apotheekbereidingen, zoals bijvoorbeeld de toevoegde waarde voor de patiënt van de apotheekbereiding, de kwaliteitsstandaarden voor productie en distributie, de handelsvergunning, productdossiers voor de productontwerpkwaliteit, en de rapportage aan de bevoegde nationale autoriteiten van relevante veiligheidskwesties. In de Resolutie apotheekbereidingen wordt een methode voor 'risico assessment' toegepast waarmee onderscheid kan worden gemaakt tussen apotheekbereidingen met respectievelijk 'laag-risico' en 'hoog-risico', op grond waarvan het juiste niveau van de kwaliteits- en veiligheidsstandaarden kan worden bepaald. Een van de aanbeveling van de Resolutie apotheekbereidingen is dat het GMP kwaliteitssysteem gebruikt dient te worden voor apotheekbereidingen met 'hoog-risico'.

De landen die de Resolutie hebben ondertekend wordt verzocht de aanbevelingen te implementeren in hun nationale wet- en regelgeving, daarbij rekening houdend met de nationale context.
Om de voortgang van de implementatie van de Resolutie apotheekbereidingen te bestuderen is een systematische review uitgevoerd in een aantal lidstaten van de Raad van Europa, welke is beschreven in **hoofdstuk 3**. De studie toonde aan dat de Europese lidstaten goede voortgang maken met de invoering van de aanbevelingen van de Resolutie apotheekbereidingen. De studie refereerde ook aan het feit dat in de EU, geneesmiddelen zijn gereguleerd door Richtlijn 2001/83/EC en Regulation (EC) No 726/2004. Deze EU wetgeving biedt weliswaar mogelijkheden voor apotheekbereidingen, maar alleen indien aan de strikte voorwaarden van deze wet- en regelgeving is voldaan. BCLA's voldoen niet (altijd) aan deze strenge voorwaarden.

Een studie naar de wetgeving inzake de bereiding van geneesmiddelen in Europese apotheken, die is gepresenteerd in **hoofdstuk 4**, toonde aan dat de beide pijlers van de wetgeving alleen van toepassing zijn waar de richtlijn 2001/83/EC zelf van toepassing is. De richtlijn is van toepassing op alle geneesmiddelen die industrieel zijn bereid of zijn geproduceerd met een methode gebaseerd op een industrieel proces, zoals is bepaald in artikel 2 (1) van Richtlijn 2001/83/EC. Dit omvat de handelsvergunning van het geneesmiddel en de fabrikantenvergunning. Producten die niet voldoen aan de condities van artikel 2 vallen niet onder de Richtlijn.

De studie toonde verder aan dat de recente interpretatie van het Europese Hof van Justitie (EHJ) inzake de reikwijdte van de EU wetgeving de juridische ruimte voor apotheekbereidingen beperkt. Het EHJ gaf een strikte interpretatie van de uitzonderingen op Richtlijn 2011/83/EC die zijn geformuleerd in artikel 3. Voor de magistrale formulae geldt dat het geneesmiddel moet zijn bereid in overeenstemming met een receptvoorschrift van een arts dat van te voren is uitgeschreven, dat wil zeggen voordat de bereiding voor de betreffende patiënt is gemaakt. Voor de officinale formulae geldt dat het geneesmiddel direct moet zijn verstrekt aan de patienten door dezelfde apotheek als die welke het geneesmiddel heeft bereid. Als gevolg hiervan, is de uitzondering voor apotheekbereidingen in de Europese wetgeving niet van toepassing op apotheken die op grote schaal bereiden en de zogenaamde magistrale formulae of officinale formulae distribueren aan andere apotheken. BCLA's worden niet genoemd in de Europese regelgeving, maar op basis van deze EHJ uitspraak moeten ze hier aan voldoen omdat de uitzonderingen voor apotheekbereidingen niet gelden voor hen. De studie toont niet of de uitzondering genoemd in artikel 5 van Richtlijn 2001/83/EU een mogelijkheid biedt voor BCLA's. Verdere studies zijn nodig om dit te onderzoeken.

In meerdere Europese lidstaten van de Raad van Europa bestaan er nationale 'oplossingen' voor BCLA's teneinde individuele gezondheidszorg mogelijk te maken waar dat nodig is en om te garanderen dat de geneesmiddelen veilig, effectief en van hoge kwaliteit zijn. Voorbeelden van nationale 'oplossingen' zijn de circulaire

in Nederland en de productievergunning voor zogenaamde 'specials' in het Verenigd Koninkrijk.

De observationele studies die zijn gedaan in Nederland, en die zijn gepresenteerd in **hoofdstuk 6 en 7**, laten zien dat de Geneesmiddelenwet is gebaseerd op European Union (EU) Richtlijn 2001/83/EC. De Geneesmiddelenwet verbiedt dat een BCLA ongeregistreerde geneesmiddelen bereidt en collegiaal doorlevert aan andere apotheken. Om de patiëntenzorg niet in gevaar te brengen, heeft de Inspectie voor de Gezondheidszorg een Circulaire inzake collegiale levering opgesteld voor alle Nederlandse apotheken. De Circulaire beschrijft de voorwaarden waaraan de BCLA's dienen te voldoen. Als een BCLA niet voldoet aan deze voorwaarden gedurende herhaalde bezoeken dan is collegiale levering van producten niet toegestaan. De voorwaarden van de Circulaire zijn: afwezigheid van een geregistreerd therapeutisch alternatief op de markt, rationele farmacotherapie, een product dossier voor alle geneesmiddelen, en voldoen aan GMP. De studies tonen aan dat de Nederlandse circulaire in voldoende mate wordt geaccepteerd en gevolgd.

Een ander terrein waar patiënt veiligheid van cruciaal belang is, is het terrein van de aseptische bereidingen van parenterale geneesmiddelen voor patiënten in instellingen voor de gezondheidszorg. Fouten bij het bereiden van deze geneesmiddelen kunnen leiden tot onmiddellijke schade voor de patiënt. Risico's die kunnen optreden bij deze aseptische bereidingsprocessen en de effecten van slechte reconstitutie praktijken zijn bestudeerd in **hoofdstuk 5.**
Deze aseptische bereidingen worden uitgevoerd in zowel apotheken als in klinische afdelingen in gezondheidszorginstellingen. In veel gevallen kunnen parenterale geneesmiddelen met een handelsvergunning niet direct aan patiënten worden toegediend, dat wil zeggen ze zijn qua presentatievorm niet gereed voor toediening. Voor toediening aan patiënten, moeten deze geneesmiddelen worden gereconstitueerd dat wil zeggen klaargemaakt of bereid. Reconstitutie heeft een speciale positie; het kan noch worden gezien als industriële bereiding noch als 'reguliere' apotheekbereiding.

De observationele studie, die in **hoofdstuk 2** is beschreven, toonde aan dat er geen of in beperkte mate wet- en regelgeving is betreffende reconstitutie van parenterale geneesmiddelen in Europa. De risico's die verbonden zijn aan de bereiding van deze geneesmiddelen en opties voor goede reconstitutie praktijken zijn bestudeerd in **hoofdstuk 5**.

Richtlijnen zijn voorgesteld voor goede reconstitutie praktijken in instellingen voor gezondheidszorg voor geneesmiddelen voor parenteraal gebruik en dit heeft geleid tot het aannemen van de Resolutie betreffende goede reconstitutie praktijken (GRP), die is aangenomen door het Comité van Ministers van de Raad van Europa op 1 Juni 2016.

De kwaliteits- en veiligheidsparameters in deze Resolutie omvatten verschillende aspecten van reconstitutie zoals bijvoorbeeld de verantwoordelijkheden van de autoriteiten en de verantwoordelijkheden van de gezondheidszorginstelling, t.w. het management, de 'designated' c.q. verantwoordelijk persoon en het personeel in de klinische afdelingen. Bovendien is een 'risk assesssment' benadering gepresenteerd die het management van de gezondheidszorginstellingen ondersteunt bij de beslissing waar in de instelling de geneesmiddelen het meest veilig kunnen worden gereconstitueerd, dat wil zeggen in de apotheek of in de klinische afdeling. Daarnaast worden er minimum eisen gesteld aan de reconstitutie in klinische afdelingen. Dit omvat bijvoorbeeld een algemene procedure voor reconstitutie voor de gehele gezondheidszorginstelling, de beschikbaarheid van gedetailleerde technische instructies voor alle geneesmiddelen, de competenties van het personeel en een goedgekeurd overzicht per afdeling van producten die mogen worden gereconstitueerd. Meer studies zijn nodig om de impact van de Resolutie betreffende goede reconstitutie praktijken in de verschillende Europese landen te bestuderen.

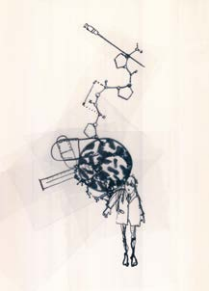
Op het terrein van de apotheekbereidingen, is een aanpassing van de regelgeving, meer specifiek van Richtlijn 2001/83/EU, noodzakelijk en urgent gezien vanuit het perspectief van de patiënt. Europese regelgeving loopt achter en schiet tekort. Het is gecreëerd in een tijd dat elke apotheker nog medicijnen bereidde in zijn of haar eigen apotheek voor zijn of haar eigen patiënten en dat grootschalige bereiding door BCLA's niet bestond. Vandaag de dag hebben veel apothekers ervoor gekozen om de eigen bereidingen stop te zetten en uit te besteden aan BCLA's.

De geharmoniseerde kwaliteits- en veiligheidsstandaarden uit 2011, gepresenteerd in **hoofdstuk 3**, en de kwaliteitsmodules van de verschillende nationale oplossingen, zoals bijvoorbeeld de Nederlandse standaarden gepresenteerd in **hoofdstuk 6 en 7**, kunnen als basis dienen voor de noodzakelijke verandering in Europese regelgeving die kan worden geconstrueerd op de reeds bestaande pilaren van productontwerp kwaliteit en productie kwaliteit.

Implicaties voor verder onderzoek werden besproken. Een gestructureerde aanpak voor verder onderzoek op het terrein van de apotheekbereidingen in Europa is aan te bevelen teneinde alle inspanningen te coördineren en te richten op het patientenbelang. Onderzoek is nodig om in kaart te brengen op welke wijze de geharmoniseerde standaarden voor kwaliteit en veiligheid van 2011 en de kwaliteitsmodules van de verschillende nationale 'oplossingen' kunnen worden gebruikt bij het creëren van een basis voor de noodzakelijke aanpassing van de Europese regelgeving. Een voorbeeld van een studie in deze context is een studie naar de condities rond de eis, die in sommige landen van kracht is, dat apotheekbereidingen niet zijn toegestaan als een geschikt farmaceutisch equivalent, met een handelsvergunning, op de markt beschikbaar is. Om de patiënt beter te kunnen bedienen, is het daarnaast van belang te onderzoeken of de verschillende nationale 'oplossingen' wel passen in het wettelijk kader. Onderzoek is nodig om te kunnen bepa-

len welke apotheekbereidingen onder welke condities in aanmerking zouden kunnen komen voor een handelsvergunning door de bevoegde autoriteiten. Onderzoek is ook nodig inzake de eis voor BCLA's om te voldoen aan GMP wat betreft de productiekwaliteit. Tevens is onderzoek nodig om te bepalen of de uitzondering van artikel 5 van Richtlijn 2001/83/EU mogelijkheden biedt voor BCLA's. Onderzoek is nodig op het belangrijke terrein van de geneesmiddelentekorten om te bepalen of, en zo ja onder welke condities, apotheekbereidingen een bijdrage kunnen leveren aan het voorkomen ervan in het belang van de patiënt en ook om te bepalen welk wettelijk kader daarvoor zou kunnen gelden.

Voor het bevorderen van de patiëntveiligheid zou het zeer waardevol zijn om verder onderzoek te doen naar de impact van de recent aangenomen standaarden voor kwaliteit en veiligheid inzake goede reconstitutie praktijken in de verschillende Europese landen.



Dankwoord

Bij het schrijven van dit onderdeel van mijn proefschrift overheerst bij mij een gevoel van dankbaarheid jegens al diegenen die mij tot hier hebben gebracht. En het zijn heel veel mensen die op de een of andere manier een bijdrage hebben geleverd aan de realisatie van dit proefschrift. Zonder al deze personen was het onderzoek niet mogelijk geweest.

Allereerst wil ik mijn promotieteam, bestaande uit mijn promotoren Prof. Dr. C. Neef en Dr. Mr. M.D.B. Schutjens en mijn co-promotor Dr. V. N. Neerup Handlos, bedanken voor de goede begeleiding en het vertrouwen dat ze in mij hebben gesteld.

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Marie-Hélène,
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Vagn,
We have worked together on an international level for many years in the fields of pharmacy preparation and the reconstitution of high-risk medication. You were a board member of the European Association of Hospital Pharmacists (EAHP) and I was the rapporteur responsible for the two fields mentioned above in the Committee of Experts (CD-P-PH/PC), coordinated by Council of Europe's European Directorate for the Quality of Medicines & Healthcare (EDQM) - together with being its Dutch delegate. Over all those years we have worked together very effectively in our different roles on the quality and safety standards for these two fields. The

cooperation with you has always been a pleasure. More recently your scientific and pharmaceutical expertise has helped me a lot in this promotion of my PhD. Many thanks for your contribution as a co-promoter.

De Inspectie voor de Gezondheidszorg ben ik zeer erkentelijk voor de ondersteuning. Met name de coördinatie door Prof. dr. P.B.M Robben heeft mijn promotietraject gefaciliteerd. Paul, veel dank voor de gesprekken en de goede begeleiding.

The support of the European Directorate for the Quality of Medicines & Healthcare (EDQM) has been essential for my thesis. I was given the opportunity to make use of the systems and structures within the organisation in order to collect the data and generate the articles for publication in scientific journals. I would also like to thank the delegates from all the other participating countries, both for their contributions in supplying the data required to enable me to undertake the published research and also for simply sharing their thoughts with me on these subjects.

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Ook wil ik de beoordelingscommissie bedanken bestaande uit Prof. Dr. H. A.J. Struijker Boudier, Prof. Dr. D.J. Touw, Prof. Dr. E. Vos en Dr. A. Vermes voor het beoordelen van het manuscript.

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Al pratend in een gezellig etablissement in Maastricht op een zondagmiddag was jij het die bij mij voor het eerst de optie om te promoveren naar voren bracht. Hiermee heb je mij gestimuleerd om dit promotietraject in te gaan. Ik blijf me na al onze mooie jaren samen nog steeds verbazen over jouw beeldend inzicht en jouw intuïtie ten aanzien van de meest uiteenlopende situaties. Dank voor je liefde, voor je geweldige ondersteuning gedurende het gehele promotietraject en je steun en

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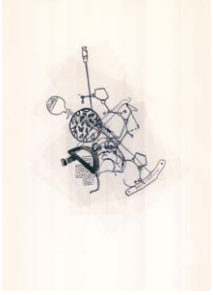

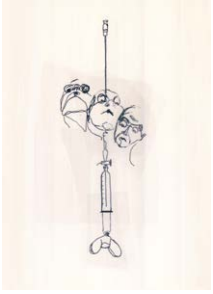

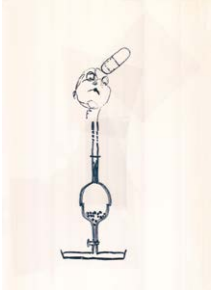

Curiculum Vitae

Henk Scheepers was born on the 25th of March 1958 in Maarheeze, the Netherlands. He obtained his secondary school diploma at the Philips van Horne Scholengemeenschap, in Weert in 1976 and went on to study Pharmaceutical Sciences at the University of Utrecht. In 1982 he obtained his Master's degree and, in 1983 he graduated as a Pharmaceutical Doctor.

Subsequently, he started working in the pharmaceutical industry where he has held management positions in research and development (R&D) and marketing (1984-1998). At Sandoz Pharmaceuticals in the Netherlands, he became clinical research associate and international project leader for research projects. He went on to work at the headquarters of Solvay Duphar in Weesp where he held the position of Medical Marketing Manager at the International Marketing Department before becoming Clinical Research Director in the R&D department.

In 1998, he joined the Dutch Health Care Inspectorate at the Ministry of Health, Welfare and Sport. There, he is currently Coordinating Specialist Senior Inspector responsible for, among other things, the surveillance of Good Manufacturing Practice (GMP) in preparing and distributing pharmacies and pharmaceutical companies. He is responsible too for the surveillance of good reconstitution practices in hospitals. Since 2013, he has also gained experience in general aspects of hospital pharmacy.

Since 2008 he has been the nominated delegate of the Netherlands for of the Committee of Experts on Quality and Safety Standards in Pharmaceutical Practices and Pharmaceutical Care (CD-P-PH/PC) at the Council of Europe in Strasbourg. Then in 2016 he became chairman of this Committee of Experts. For this Committee he is the rapporteur responsible for the regulation of practices in the fields of pharmacy preparation for the special needs of patients and the reconstitution of high-risk medication, respectively. Consensus has now been reached in both areas concerning resolutions containing harmonised quality and safety standards. The Resolutions were adopted by the Committee of Ministers of the Council of Europe in 2011 and 2016, respectively (Resolution CM/ResAP(2011)1; Resolution CM/Res(2016)2).

Both in the pharmaceutical industry as in the Dutch Health Care Inspectorate, his roles have encompassed national and international tasks.