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.

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.

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 the article by Scheepers *et al*.[4]

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 UK.

Details of the survey questionnaire are included in an online supplementary 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.

RESULTS

The results relating to practice and legislation in 12 member states were collected and are presented in table 1. 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 is not binding legally and is less stringent than, for example, a European Directive. The most relevant comments made by the countries are presented in this section.

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

The value of pharmacy preparations and the responsibility of healthcare 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 NL it is not allowed for these PDPs to prepare and distribute a medicinal product if a licensed pharmacotherapeutic alternative is available on the

Table 1 Summary table

Resolution pharmacy preparation	1 BE	2 DK	3 F	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) (Good manufacturing practice 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)													
Good distribution practice 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.

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 CZ, a quality system comparable to the PIC/S GPP Guide applies in cases of high-risk preparations. In IT, a higher-quality standard that approximates to GMP is required for sterile production. In CH 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 PL, 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 DK 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 NL, 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 CH, 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 PT the recommendation is under consideration. In BE, Finland, DK 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, DK, Finland, PL, the NL and IT, 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 BE 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 DK, 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) fulfil these strict conditions. The legal aspects are addressed and explained the article by Scheepers *et al*.[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 IE, a notification system does not exist for pharmacies, but for holders of a special 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 report that they have implemented an inventory or an alternative. In DK 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 (GDPs)

The Resolution states that pharmacies or companies preparing medicinal products under their responsibility upon the request of pharmacies should comply with GDP.

This is currently the case in nine out of the 12 respondent countries. BE, the CZ and IE 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 DK, the UK, IE and CH some export or import occurs, but this is mainly to cover individual patient's needs, which is allowed for in the Resolution.

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 NL, 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 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 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 USA.[7–9]

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 protecting 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

What this paper adds?

What is already known on this subject?

- 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.
- 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?

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

results of the survey indicate that among the countries involved, there is, in general, a clear commitment to implement the recommendations of the Resolution.

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