

**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)*

The Committee of Ministers, in its composition restricted to the representatives of the States Parties to the Convention on the Elaboration of a European Pharmacopoeia (ETS No. 50),¹

Considering that the aim of the Council of Europe is to achieve greater unity between its members and this aim may be pursued, among others, by common action in the public health field including the adoption of common regulations;

Having regard to the standard-setting carried out under the Convention on the Elaboration of a European Pharmacopoeia and its Protocol (ETS No. 134) which endeavours to promote progress in every way possible, both in the social field and the related field of public health through the harmonisation of specifications for medicinal substances, which, in their original state or in the form of pharmaceutical preparations, are of general interest and importance to the peoples of Europe;

Underlining the need to apply where possible relevant international standards, such as those developed by the World Health Organization and the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S);

Recalling also the chapters and monographs of the European Pharmacopoeia containing general and specific requirements applicable to medicinal products prepared in pharmacies, in particular about standards and methods for the control of the chemical, pharmaceutical and microbiological quality of active substances and excipients, about dosage forms and containers;

Bearing in mind the measures proposed in the Committee of Ministers' Resolution ResAP(93)1 on the role and training of community pharmacists, Resolution ResAP(94)1 on the rational use of medicines and Resolution ResAP(97)2 on the development of the function of pharmacists and the adaptation of their initial training, and the need to implement them;

Recalling the measures proposed in the Committee of Ministers' Resolution ResAP(2001)2 concerning the pharmacist's role in the framework of health security, *inter alia* emphasising that community pharmacists are the health professionals most readily accessible to patients and that they help to personalise the delivery of patient care;

Bearing in mind the results of the international symposium "European co-operation and synergy in quality standards beyond the European Pharmacopoeia", held on 15 and 16 June 2007, and of the expert workshop "Promoting standards for the quality and safety assurance of pharmacy-prepared medicinal products for the needs of patients", held on 24 September 2009 at the European Directorate for the Quality of Medicines & Health Care (EDQM), Council of Europe, in Strasbourg;

Considering that medicinal products manufactured by the pharmaceutical industry are not always authorised or available to cover the special needs of individual patients;

¹ States concerned: Austria, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Montenegro, Netherlands, Norway, Poland, Portugal, Romania, Serbia, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, "the former Yugoslav Republic of Macedonia", Turkey, Ukraine and United Kingdom.

Noting that medicinal products manufactured on an industrial scale must obtain marketing authorisation issued by the competent regulatory authority before being placed on the market;

Considering that the preparation of medicinal products in pharmacies, which may be required as a consequence of the individual or medical condition of the patient in the absence or unavailability of appropriate medicinal products on the market, is indispensable for accommodating the special needs of individual patients in Europe;

Noting that the preparation of medicinal products in pharmacies is not harmonised throughout Europe and falls under the national competencies of the States Parties to the Convention on the Elaboration of a European Pharmacopoeia;

Considering that pharmacists can legally prepare medicinal products in the pharmacy by virtue of their professional education, professional licence and licensing of the pharmacy's premises;

Emphasising that patient safety and the achievement of the therapeutic aim require that medicinal products prepared in pharmacies meet appropriate and specific criteria for quality, safety and added value also where no marketing authorisation is required;

Underlining that the requirements for the quality and safety assurance of medicinal products prepared in pharmacies through specific structures and processes, in addition to the relevant pharmacopoeial requirements, are necessary for ensuring appropriate patient safety in Europe and the added value of the preparation of such medicinal products in pharmacies;

With a view to avoiding quality and safety differences between medicinal products prepared in pharmacies and those prepared on an industrial scale, recommends that the governments of the States Parties to the Convention on the Elaboration of a European Pharmacopoeia adapt their regulations in accordance with the principles set out in the present resolution:

- added value of pharmacy preparations and responsibilities of health care professionals;
- preparation process;
- product dossier;
- marketing authorisation;
- labelling;
- compliance with pharmacopoeial requirements;
- reconstitution of medicinal products;
- authorisation for pharmacies or, if not covered by other national legislation or guidance, licences for companies making preparations for pharmacies;
- transparency and safety;
- rational use;
- surveillance;
- communication and information to patients;
- distribution of pharmacy preparations.

In order to implement the present resolution, States Parties to the Convention on the Elaboration of a European Pharmacopoeia should supplement it through additional practical guidance, taking into account the national frameworks.

Appendix to Resolution CM/Res(2016)1

1. Field of application

This resolution covers medicinal products for human use only. Other products, such as medical devices or cosmetic products are outside the scope of this resolution.

This resolution applies to pharmacy preparations also known as unlicensed pharmaceutical preparations, i.e. medicinal products which are prepared for the special needs of patients by community and hospital pharmacies and to comparable processes and preparations of medicinal products as referred to in paragraph 10.2. It applies also to the reconstitution of medicinal products in health care establishments.

The provisions cover all pharmacy preparations, both extemporaneous and for stock, and their applicability depends on the outcome of the risk-assessment of the pharmacy preparation.

2. Definitions

Good distribution practices (GDP): practices as specified in the European Commission “Guidelines on good distribution practice of medicinal products for human use” (94/C 63/03).

Good manufacturing practices (GMP): practices as specified in European Commission Directive 2003/94/EC and EudraLex, Volume 4, on Guidelines for good manufacturing practices for medicines for human and veterinary use.

Good preparation practices (PIC/S GPP): “Guide to good practices for the preparation of medicinal products in health care establishments”, in Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) Guide PE 010.

External supply (see note 1, model procedure for risk assessment): any supply of pharmacy preparations by the preparing pharmacy other than directly to patients.

Internal supply (see note 1, model procedure for risk assessment): the direct supply of pharmacy preparations to patients by the preparing pharmacy.

Pharmaceutical equivalent: a medicinal product having the same active substances, irrespective of the excipients used, the same or similar intended purpose, equivalent strength and posology, and the same or similar route of administration.

Dispensing pharmacy: the pharmacy which receives the prescription for a patient and which provides the pharmacy preparation to the patient (often, the preparing and the dispensing pharmacies are identical).

Preparing pharmacy: produces the pharmacy preparation for a dispensing pharmacy (often, the preparing and the dispensing pharmacies are the same).

Clinical area: areas in healthcare establishments where patients receive treatment, such as wards, ambulatory care settings and operating theatres.

Closed-system procedure for sterile medicinal products: a procedure whereby a sterile medicinal product is prepared by transferring sterile starting materials or solutions to a pre-sterilised sealed container, either directly or by using a sterile transfer device, and without exposing the solution to the external environment (such as intravenous infusion services: services for cytotoxic medical products or total parenteral nutrition (TPN)).

Open-system procedure for sterile medicinal products: a procedure whereby a sterile medicinal product is prepared and the solution is exposed to the external environment.

Reconstitution: manipulation to enable the use or administration of a medicinal product. For products with a marketing authorisation issued by any competent medicines regulatory authority the reconstitution is carried out in accordance with the instructions given in the summary of product characteristics (SmPC) or the patient information leaflet.

3. Added value of pharmacy preparations and responsibilities of health care professionals

Pharmacy preparations are of added value if, due to medical, pharmaceutical or personal reasons, they are needed by a specific patient or by specific population groups with particular needs.

3.1. *Pharmaceutical equivalents on the national market*

Pharmacy preparations are not advisable if a suitable pharmaceutical equivalent with a marketing authorisation is available. Before preparation, the pharmacist should verify whether a pharmaceutical equivalent is available on the national market, taking into consideration the pharmaceutical form and the strength.

3.2. *Added value and responsibility of health care professionals*

The professionals involved in patient care should jointly assume responsibility for determining whether a pharmacy preparation could be of added value. They should take into account the medical need of the

patient. A pharmacist should be able to refuse a prescription for a pharmacy preparation if a suitable pharmaceutical equivalent is available on the national market, inform the physician that a suitable pharmaceutical equivalent is available and discuss with the physician if there is a specific need to dispense a pharmacy preparation.

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. Pharmacy preparations should always be distributed by a dispensing pharmacy because this pharmacy receives the prescription for the patient. The preparing pharmacy should be responsible for ensuring that an appropriate quality assurance system is in place.

4. Preparation process

All pharmacy-prepared medicinal products should be prepared using an appropriate quality assurance system. Before preparation, a risk assessment should always be carried out in order to define the level of the quality assurance system which should be applied to the preparation of the medicinal product.

A possible model procedure for risk assessment, described in section 5.2 and in note 1, provides an aid to distinguishing between two risk levels ("high-risk preparations" and "low-risk preparations") and between two levels of quality system based on a risk-graded application of quality assurance principles.

It is recommended that the GMP Guide be used as a reference for an appropriate quality system for "high-risk preparations", and that the PIC/S GPP Guide be used for "low-risk preparations". The application of other guidelines with an equivalent quality level is possible, depending on the national legislation or guidance.

Premises, facilities and pharmaceutical knowledge should be appropriate for the preparation of the medicinal product.

5. Product dossier

Product dossiers, as described in note 2, should be required only for stock preparations.

For extemporaneous preparations, it will not usually be possible to compile a complete product dossier containing all possible information mentioned in section 5.1. as it could lead to a delay in the supply of necessary medicines. For extemporaneous preparations, however, the pharmacist and the prescriber should always consider the risks for the patient, which include the risks posed by a medicinal product without documentation specifying the added value of the pharmacy preparation and the quality assurance system applied to its production, versus the risks related to the unavailability of this medicinal product.

5.1 Topics to be covered by a product dossier

The pharmacy should ensure a good balance between all possible disadvantages and the added value of the pharmacy preparation. The product-specific quality properties, as well as the site-specific manufacturing conditions of the preparation should be specified in a product dossier.

A product dossier should cover the following topics:

- a. demonstration of the added value of the pharmacy preparation;
- b. demonstration that the active pharmaceutical ingredients, excipients and containers meet relevant requirements, taking into account specific patient needs;
- c. description of the preparation process including, where appropriate, testing;
- d. development and background documentation of the preparation process;
- e. use of the product including information for the patient and the prescriber.

The contents and detail of information as mentioned in points a to e above depend on the risk assessment, which should be documented. The product dossier should be more comprehensive for preparations that carry a higher risk than for those carrying a lower risk.

This is taken into account by the model procedure for risk assessment, see note 1.

Alternative risk assessment methods may be applied, provided that an appropriate assessment of the risk is obtained.

More details about the product dossier can be found in note 2.

5.2. *Risk assessment of a pharmacy preparation*

When making a pharmacy preparation, the pharmacist should always undertake an appropriate risk assessment in order to determine the level of the quality system which should be applied to the preparation of the medicinal product.

This risk assessment should consider:

- a. dosage form and administration route;
- b. amount prepared;
- c. pharmacological effect of the medicinal product for the envisaged route of administration;
- d. therapeutical window (dose range for therapeutic doses);
- e. type of preparation process;
- f. supply.

The risk assessment should consider the contribution of active pharmaceutical ingredients and excipients to the safety profile of the pharmacy preparation.

Where appropriate, active pharmaceutical ingredients manufactured according to GMP and analysed according to pharmacopoeial standards should be used.

A risk assessment model can be found in note 1.

5.3. *Availability of data for authorities for inspection or upon request*

Pharmacies should have chemical, pharmaceutical and microbiological data or information (see section 5.1, a-e), as applicable, concerning the pharmacy preparations available for inspection or upon request of the authorities.

The production of different batches should be documented in individual batch records, which should be included in the product dossier.

6. **Marketing authorisation**

If the preparation is carried out on a scale comparable to the industrial level, if distribution takes place and if an authorised medicinal product, or a pharmaceutical equivalent (see section 3.1), is on the market, the competent drug regulatory authorities should consider establishing, if they have not already done so, the requirement for obtaining a marketing authorisation, including full compliance with GMP, for pharmacy preparations (see note 1: refer to "high-risk preparation").

7. **Labelling**

Correct labelling is essential for patient safety. The label should present the following information, as appropriate:

- a. name, address and telephone number of the dispensing pharmacy;
- b. name and address of the preparing pharmacy;
- c. name of the pharmacy preparation, if applicable;
- d. full qualitative composition and the quantity of the active substance;
- e. batch number, if applicable;
- f. expiry date or information about limits for use;
- g. special storage conditions or handling precautions;
- h. directions for use, warnings and precautions;
- i. route of administration.

8. **Compliance with pharmacopoeial requirements**

When a pharmacy preparation is needed and if it is applicable, a standard formula should be found in a national pharmacopoeia or nationally recognised formularies.

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 of a State Party to the Convention on the Elaboration of a European Pharmacopoeia.

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

9. Reconstitution of medicinal products in health care establishments

In general, 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. Reconstitution considered to be low risk can be done on the wards. If the residual risk² has been assessed systematically (see Note "Checklist for the identification, assessment and reduction of risk posed by the reconstitution of medicinal products in clinical areas", Resolution CM/Res(2016)2 on good reconstitution practices in health care establishments for medicinal products for parenteral use), the health care establishment could decide on and document whether or not a medicinal product is suitable for reconstitution in a particular clinical area.

9.1. Responsibilities of the health care establishment

The health care establishment should decide and document decisions on reconstitution in line with Resolution CM/Res(2016)2 on good reconstitution practices in health care establishments for medicinal products for parenteral use.

9.2. Role of the authorities

As reconstitution is not generally considered a process in the context of pharmacy preparations, national responsible authorities should develop, in co-operation with the relevant professional bodies, specific legislation and guidance taking into consideration the provisions set out in Resolution CM/Res(2016)2 on good reconstitution practices in health care establishments for medicinal products for parenteral use.

10. Authorisation for pharmacies or licences for companies making preparations for pharmacies

10.1. Authorisation for pharmacies

In general, authorisation by the competent authorities or bodies is a prerequisite for a pharmacy to carry out operations.

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.

10.2. Licence for companies

In some countries, the preparation of medicinal products is performed at the request of pharmacies by companies which 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.

11. Transparency and safety

11.1. Reporting of quality and safety issues

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.

11.2. Notification or announcement system

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.

² Dimension of risk and the effectiveness of risk reduction methods in place.

11.3. *Inventory for pharmacy preparations*

With a view to transparency as regards pharmacy preparations for stock, the establishment of national inventories is encouraged.

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.

11.4. *Rational use*

Based on clinical criteria, member States should be encouraged to engage with clinical experts on rational use of the medicines established in the inventory.

11.5. *Surveillance*

Based on the information obtained through the above-mentioned notification system, the competent authorities should perform risk-based inspections.

Competent authorities should have powers to suspend preparation activities.

12. **Communication and information to patients**

Communication to patients and carers of patients receiving pharmacy preparations is of crucial importance.

12.1 *Information about the pharmacy preparation*

Essential information should be given to the patient, if available, based on the product dossier. A leaflet containing product-specific information to patients is not needed for pharmacy preparations. General information to patients concerning the therapy and the use of the pharmacy preparation is recommended, including indications in some specific cases.

13. **Distribution of pharmacy preparations**

13.1. *Compliance with good distribution practices (GDP)*

Pharmacies or companies preparing medicinal products under their responsibility upon the request of pharmacies should comply with good distribution practices (GDP).

13.2. *Export/import of pharmacy preparations*

Other than to meet an individual patient's needs, export/import, of pharmacy preparations from a State Party to the Convention on the Elaboration of a European Pharmacopoeia to other States Parties 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.

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Note 1: Model procedure for risk assessment

This is a proposed model for risk assessment as to whether a pharmacy preparation carries a high or a low risk as referred to in this resolution. Alternative risk-assessment methods may be applied provided that an appropriate assessment of the risk is obtained.

The risk assessment should also consider the contribution of the active pharmaceutical ingredients, excipients and containers to the safety profile of the pharmacy preparation.

Under the following sections 1 to 5, the decision criteria for the risk assessment of pharmacy preparations are specified. Each decision criterion has a graded risk factor ranging from 1 to 5. The multiplication of these risk factors results in a number, which indicates the level of the quality system required for the pharmacy preparation process. If the number is higher than 100, the preparation is considered a "high-risk preparation"; if the number is equal to or lower than 100, it is considered a "low-risk preparation". It is

recommended that the GMP Guide be used as a reference for an appropriate quality system for “high-risk preparations”, and that the GPP Guide be used for “low-risk preparations”. The application of other guidelines with an equivalent quality level is possible, depending on national legislation or guidance.

Risk-based decision matrix

1. Type of preparation

| | | |
|----|--|-----|
| a. | parenteral preparations | = 5 |
| b. | eye preparations used in trauma or surgery | = 4 |
| c. | preparations for inhalation | = 4 |
| d. | dosage forms for sterile digestive administration (such as oral, sublingual and rectal administration) | = 4 |
| e. | cutaneous and transdermal preparations | = 4 |
| f. | dosage forms for digestive administration (such as oral, sublingual and rectal administration) | = 3 |
| g. | eye preparations used on the intact eye | = 1 |
| h. | cutaneous and transdermal preparations/dosage forms where sterility is not required | = 1 |

2. Amount prepared annually (units)

Depending on the type of preparation and the amount prepared annually, a risk factor between 1 and 5 should be determined, taking into account national legislation or guidance. It is recommended to define a separate set of risk factors (1-5) for the following types of preparation, with a risk factor of 1 for very small amounts:

- liquid preparations and solid preparations (e.g. powders);
- oral preparations (solid dosage forms);
- rectal preparations;
- cutaneous and transdermal preparations;
- eye preparations.

3. Pharmacological effect of the active substances

| | | |
|----|-------------|-----|
| a. | very strong | = 5 |
| b. | strong | = 3 |
| c. | mild | = 1 |

While grading the pharmacological effect of the active substances, the following criteria should be considered: absence of a pharmacopoeial monograph at European level or at the level of a State Party to the Convention on the Elaboration of a European Pharmacopoeia, carcinogenetic properties, mutagenic properties, ecological toxicity, risk of allergy, therapeutic window, dosage, stability (light, O₂, temperature, pH changes), and chemical, pharmaceutical and microbiological quality.

4. Preparation process

| | | |
|----|--|-----|
| a. | aseptic filling | = 5 |
| b. | terminal sterilisation | = 4 |
| c. | dissolving, mixing not for the purpose of reconstitution | = 2 |
| d. | diluting not for the purpose of reconstitution | = 2 |
| e. | filling only (non-sterile product) | = 1 |

5. Supply

| | | |
|----|-----------------------------------|-----|
| a. | external only | = 5 |
| b. | mainly external (I:E ≈ 1:2) | = 4 |
| c. | internal and external (I:E ≈ 1:1) | = 3 |
| d. | mainly internal (I:E ≈ 2:1) | = 2 |
| e. | internal only | = 1 |

Note 2: List of topics to be covered in a product dossier, depending on the results of the risk assessment for pharmacy preparations

1. Added value and preparation process of the pharmacy preparation
 - a. description of the final preparation process;
 - b. demonstration of the added value of the pharmacy preparation.
2. Composition
 - a. function;
 - b. demonstration that the active pharmaceutical ingredients, excipients and containers meet relevant requirements, taking into account specific patient needs;
 - c. specifications and traceability of origin of the starting materials;
 - d. specifications of the primary packaging material, etc.
3. In-process controls and quality controls of the finished product
 - a. product specific procedures;
 - b. records of prepared batches.
4. In-process controls and quality control of the finished product
 - a. sampling;
 - b. analytical methods;
 - c. acceptance criteria, etc.
5. Results of test batches (namely, information on the development, background and evaluation of the preparation process, including testing)
6. Validation
 - a. of the preparation process;
 - b. of analytical methods.
7. Stability considerations
 - a. a plan for own stability studies;
 - b. the evaluation of stability data, etc.
8. Use of the product and information for the patient.