Monographs of the European Drug Shortages Formulary - Framework

General considerations

The preparation of unlicensed pharmaceutical preparations is, in certain situations, an efficient tool to mitigate the negative effects of the shortage of licensed medicines. However, in the event of a medicine shortage and before considering the use of unlicensed pharmaceutical preparations – as defined in the European Pharmacopoeia (Ph. Eur.) general monograph on *Pharmaceutical preparations* (*2619*) – preference should always be given to:

1. Licensed medicinal products that have been assessed by a regulatory agency
2. Licensed medicinal products that have been assessed by a foreign regulatory agency and have been imported
3. Alternative licensed medicinal products that have been assessed by a regulatory agency

As per Resolution CM/Res (2016)1 of the Council of Europe on quality and safety assurance requirements for medicinal products prepared in pharmacies for the special needs of patients, it is crucial that:

"*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."*

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

"For extemporaneous preparations, […], 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. "

Unlicensed pharmaceutical preparations are defined according to the European Pharmacopoeia (Ph. Eur.) general monograph on Pharmaceutical preparations (2619).

Prioritisation and inclusion criteria for a formulation

The decision to include a formulation in the European Drug Shortages Formulary (EDSForm) requires careful consideration of some or all the following criteria:

1. Clinical benefits: priority should be given to the inclusion and evaluation of formulations of medicinal substances listed as critical or essential in the member states (possible input: national or EU lists of critical medicines)
2. Expected supply vulnerability: priority should be given to the inclusion and evaluation of monographs of substances that are most at risk of shortage in the member states (possible input: analysis of supply chain vulnerability by institutional actors) or that are used by a significant part of a vulnerable part of the population (possible input: market share data)

3. Feasibility: the formulary should only include formulations that are feasible in a hospital/community pharmacy environment from a technical/safety standpoint (possible input: the EDQM's Methodological guide to select medicines at risk of shortages). The availability of API(s) described in a formulation in the member states should be evaluated and taken into account.
4. Composition of the formulation: candidate formulations for inclusion in the formulary should be safe and suitable for the targeted groups of patients; insofar as is possible, excipients of concern are to be avoided. Formulations containing proprietary, commercial, non-pharmacopoeial, ready-to-use excipients (e.g. complex pharmaceutical vehicles) should not be included in the formulary.

   A preferred preparation has the following features:

   - The dosage form is appropriate for the target group (e.g. acceptability, palatability).
   - When applicable, pH and osmolality have been investigated and should be appropriate for the route and method of administration and the age of the target group.
   - Bioavailability data is available.

Selected formulations are to be drafted into monographs to be included in the European Drug Shortages Formulary. EDSForm monographs describe preparation steps involved in the production of the formulations and quality control thereof.

NOTE: The work programme should be run in co-ordination with the relevant working groups (e.g. PaedF working party) in an effort to avoid duplication of effort.

Use of the monographs of the European Drug Shortages Formulary

EDSForm monographs are intended to be used to mitigate shortages of essential medicines. To this end, the monographs describe production steps and associated quality controls that should enable the preparation of standardised, unlicensed pharmaceutical preparations (as defined in Ph. Eur. general monograph *2619*, *Pharmaceutical preparations*).
Unless otherwise stated in the individual monographs, the instructions given in the monographs cover the preparation of both stock and extemporaneous preparations.

The pharmacist or responsible person intending to use a monograph of the EDSForm should first perform an initial risk assessment related to the production of the described formulation.

This initial risk assessment should take into account, *inter alia*, the following aspects:

- Intended use of the monograph (e.g. for the production of extemporaneous or stock preparations)
- Batch size
- Safety of the active substance
- Production equipment/facilities
- Signals from national and supranational pharmacovigilance systems
- Concerns about active substances with a low therapeutic index (e.g. regarding age, pharmacokinetics)
- Dosage form
- Nature of the product (e.g. sterile or non-sterile)
- Ethical considerations
- National or supranational regulations

Preparation steps, in-process controls and analytical procedures described in monographs of the formulary should be carried out by the pharmacist or responsible person based on the outcome of the initial risk assessment.

It is wholly the responsibility of the pharmacist or the responsible person using part or all of an EDSForm monograph to ensure that the resulting pharmaceutical preparations comply with the requirements of the Ph. Eur. (e.g. general monograph *2619*, *Pharmaceutical preparations*) and national/supranational regulations.

Overview of the monographs

EDSForm monographs describe the preparation steps, in-process controls and analytical procedures involved in producing a formulation.

The preparation steps and in-process controls are intended to ensure the repeatability and safety of production. They take into account well-established guidelines (e.g. relevant PIC/S guide, relevant ICH guidelines). Analytical procedures are described to help ensure that the resulting products comply with the specifications of the monograph.

Monographs include suitable analytical procedures and acceptance criteria. Analytical procedures such as appearance, identity, dissolution and purity tests, uniformity and microbiological tests, are described when and if relevant. The suitability of analytical procedures described in a monograph is verified and validated, taking to account the requirements of the European Pharmacopoeia (see Ph. Eur. general monograph on *Pharmaceutical preparations (2619))*, and the relevant ICH guidelines.

General content of the monographs

The structure and content of EDSForm monographs are described below.

Explanations are given in italic type

DEFINITION
The definition section lists each active pharmaceutical ingredient (API) with the specific salt form, the pharmaceutical form, dosage strength, and the upper and lower percentage content limits for each.
When relevant, the ATC code of the APIs, with reference to the medicinal product the monograph covers, is specified.

REFERENCES TO MONOGRAPHS
Active(s) substance(s)
The specific salt and any relevant information (e.g. specific grade, crystalline form, CAS number) are specified for each active substance.
A reference to the corresponding Ph. Eur. monograph should be given.

Excipients
The specific salt and any relevant information (e.g. specific grade, CAS number) are specified for each excipient. A reference to the corresponding Ph. Eur. monograph should be given.

Pharmaceutical form
A reference to the corresponding Ph. Eur. general monograph should be given.

FORMULATION
The formulations will be evaluated and drafted in an EDSForm monograph by the expert group, based on the following:

1. All excipients are necessary, suitable for their function and compatible in the final product.
2. All excipients should be risk-assessed in relation to the patient group, severity of the disease, exposure and availability of alternative treatments. *If the monograph is seen as appropriate*

and necessary for a subset of patients, restrictions related to the use of specific excipients are flagged in the monograph.

3. The qualitative and quantitative composition (active substances, excipients, and their amount) is given in a bibliographic reference having been evaluated by the expert group.
4. The active substances and excipients used in the preparation meet the requirements of the Ph. Eur. monograph *Substances for pharmaceutical use* (*2034*) and, if available, of the related individual monographs.
5. Active substances and excipients used in the preparation that have a substance-specific Ph. Eur. or national monograph are to be preferred. *Active substances and excipients not covered by a Ph. Eur. or national monograph are to be considered on a case-by-case basis, taking into account the intended use and the risk involved.*

If the therapeutic index is low, great care is taken to ensure that application of suitable quality criteria provides a guarantee that the prepared product will be safe and effective.

SAFETY CONSIDERATIONS

When relevant, the hazard classification of the active(s) substance(s) should be indicated according to e.g. regulation EC No. 1272/2008 (CLP) or any other relevant regulation.
When relevant, the hazard pictograms, the signal word, the hazard statements, and the precautionary statements should be indicated.

NOTE: The safety equipment and protocols (personal and collective) to be used in relation to a specific risk should be implemented by the pharmacist or the responsible person in accordance with national or supranational requirements.

PRODUCTION

1. The preparation process is described in such a way that the quality of the product is ensured in accordance with the corresponding Ph. Eur. dosage form monograph.
2. The description of the process ensures that the preparation process is reproducible.
3. Suitable in-process controls may be described after critical steps in the preparation process to verify that the quality is maintained.

NOTE: The preparation should be produced taking into account the outcome of the initial risk assessment (see above). If necessary, the potential for cross-contamination, the validation process and the need for dedicated equipment and premises should be evaluated. Personnel should be trained as defined in national or supranational procedures.

ADDITIONAL INFORMATIONS

Monographs should include any information that helps the pharmacist or responsible person to assess the risks related to the production of the formulation.

CHARACTERS OF THE FINAL PRODUCT

The appearance and colour of the final product should be described.

LABEL

The final product should be labelled in accordance with national and supranational regulations.

ANALYTICAL PROCEDURES

When and where appropriate, monographs describe validated analytical procedures that are suitable for batch release. When relevant, analytical procedures that are suitable for in-process controls are described. The suitability of all analytical procedures described in the monographs is assessed by the experts.

NOTE: For extemporaneous preparations, simple analytical procedures (e.g. non-instrumental methods) may be useful and sufficient. Users may employ other suitable methods to ensure that the appropriate quality is achieved in accordance with the initial risk assessment carried out and any national or supranational guidance or legal requirements. Analytical procedures should be implemented in

accordance with the requirements of the general monographs and general monographs on dosage forms of the Ph. Eur.

STABILITY OF THE FINAL PRODUCT

Available data on the physical, chemical, and microbiological stability of the formulations should be assessed by the experts, taking into account best practices, guidelines and available data. When and if necessary, the experts may complete the existing data set by performing the relevant experimental verifications.

Available and complementary data may be used to assign a shelf life to the formulation described.

The stability assessment should cover the following:

1. Containers and container closure systems: pharmacopeial quality materials are used for if a corresponding monograph is available. The container system should be described in the monograph.
2. Evaluation of the chemical, physical and microbiological stability of preparations, stating the shelf life and storage conditions with the container closure system used. Stability data is given in relation with the container system used.
3. Data for in use stability, if available.

STORAGE

The monograph indicates:

1. The shelf life and the relevant storage conditions (e.g. temperature, relative humidity, protection from light).
2. When available, the in-use shelf life and the storage conditions after opening.

Vigilance and maintenance of monographs

It is essential to re-evaluate all monographs published in the European Drug Shortages Formulary to keep the formulary up to date with current clinical, scientific and regulatory developments.

ACTIVE MONITORING BY THE GROUP

The following should be monitored regularly and their potential impact (revision or suppression) on a published monograph assessed:

- EMA's Pharmacovigilance Risk Assessment Committee (PRAC) recommendations concerning active substances;
- European guidelines on excipients;

FOLLOW-UP AND EVALUATION OF INFORMATION RECEIVED

Revision or suppression of a monograph should be considered when information of the following type is received:

- Safety signals other than from EMA PRAC;
- Quality issues;
- New, evidence-based clinical use;
- Follow-up from questions received by the EDQM.

Stakeholders may request changes based on information known to them (e.g. published literature, changes in clinical practice).

PERIODICAL RE-EVALUATION

All monographs should be reviewed at the latest after five years.

A periodical re-evaluation should include:

1. Checking to ensure that current clinical/therapeutic criteria for inclusion of a monograph in the formulary are still met.
   Criteria for inclusion in the formulary may change in the future. Older monographs need to be updated in view of these changes. There may have been a change in the therapeutic guidelines, so that the recommended use (e.g. indication, type of use, age) of the product differs, a new first-line treatment may be available, or the treatment of the disease has changed.
2. Checking to ensure that current quality criteria for inclusion are still met.
   The state-of-the-art for the production, testing and assay of extemporaneous preparations may change. Published monographs should keep pace with these developments.
3. A review of relevant feedback on the monograph received by the EDQM.
4. Screening for changes in other existing formularies that were used as the basis for elaboration.
5. Checking in other formularies for changes that have been developed and would be more suitable, practical and/or documented.