

Annex 6

Good pharmacopoeial practices: Chapter on monographs for compounded preparations

Background

Following the fiftieth meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations, the guidance on good pharmacopoeial practices (GPhP) was published as Annex 1 to the report.¹ The primary objective of the GPhP is to define approaches and policies in establishing pharmacopoeial standards with the ultimate goal of harmonization. In line with this objective, this guidance on monographs for compounded preparations has been developed outlining the structure and contents of such monographs.

1. Introduction

Compounded preparations² involve the preparation, mixing, assembling, altering, packaging and labelling of a medicine or drug-delivery device, in accordance with a licensed practitioner's prescription, medication order or initiative based on the relationship between the practitioner, patient, pharmacist and compounder in the course of professional practice.

This section of the GPhP helps define good practices for developing pharmacopoeial monographs for compounded preparations, which will help ensure the quality of these preparations.

2. Monograph development

Pharmacopoeial monographs for compounded preparations are generally developed by a pharmacopoeia and its expert committees rather than by donation from a manufacturer. Monographs for compounded preparations may include a stability-indicating assay and acceptable limits for the active pharmaceutical ingredient(s) (API(s)). Where required, a beyond-use date (BUD) or assigned

¹ Good pharmacopoeial practices. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fiftieth report. Geneva: World Health Organization; 2016: Annex 1 (WHO Technical Report Series, No. 996).

² The term "compounded preparations" is used throughout this document. This term encompasses medicines that are (i) prepared extemporaneously, under the supervision of a pharmacist, for a specific patient and (ii) those that are prepared in advance in appropriate facilities (also known as stock preparations).

shelf life³ is included, based on suitable stability studies. Typical sources of pharmacopoeial monographs for compounded preparations include:

- laboratory-conducted method development, validation and stability studies;
- peer-reviewed literature, evaluated based on stringent criteria;
- donated scientific data.

3. Quality of ingredients

Ingredients specified in the definition and/or used in the formula in pharmacopoeial monographs for compounded preparations comply with relevant monographs for pharmaceutical substances and general monographs, if available.

4. Monograph title

The titles of monographs for compounded preparations will follow national naming conventions, but should include the name of the pharmaceutical substance and the dosage form. Some pharmacopoeias may use the following naming convention for compounded preparations that are used for both humans and animals:

- [medicine name] dosage form;
- [medicine name] compounded [route] [dosage form];
- [medicine name] compounded [route] [dosage form], veterinary (for animals only).

5. Sections of the compounded preparation monograph

Compounded preparation monographs may include the following sections:

- Definition and content
- Assay
- Compounding procedures
- Identification tests
- Specific tests
- Additional information
- Stability information and BUD

³ The term “beyond-use date” (BUD) is used throughout this document synonymously with “assigned shelf life”.

5.1 Definition and content

Assay limits provide the acceptable range of the labelled amount of the API(s). The assay limits should take into account the precision and accuracy of the method, the strength of the preparation and the stability of the pharmaceutical substance in the specific preparation. Assay limits are normally expressed with reference to the active moiety or the label claim, in accordance with national and regional requirements.

5.2 Assay

The assay quantifies the amount of API in the compounded preparation. It may also quantify certain excipients, such as preservatives, depending on national and regional legislation. In certain cases more than one assay method may be necessary, for example, where the preparation contains more than one API.

Where required, the compounded preparation should be tested for strength and potency. The purpose of strength or potency testing is to establish or verify the concentration of the pharmaceutical substance(s) in the compounded preparation.

Where possible, a validated stability-indicating assay method is described. Methods used generally include high-performance liquid chromatography or gas chromatography, among others. Other methods include titration and microbiological assays, which are sometimes used to test antibiotics.

The routine testing of each batch may not be feasible.

5.3 Compounding procedures

The monograph may contain a formula for the preparation which lists all of the ingredients and their quantities. Compounding procedures may include all of the steps necessary to accurately and reproducibly prepare the preparation.

5.4 Identification tests

The tests given in the identification section are not designed to give a full confirmation of the chemical structure or composition of the API(s) in the compounded preparation. They are intended to give confirmation, with an acceptable degree of assurance, that the API(s) in the compounded preparation is/are the one(s) stated on the label.

5.5 Specific tests

In addition, specific tests may be included, as appropriate. Examples are included in the following list, which is neither exhaustive nor comprehensive:

- pH;
- sterility;

- bacterial endotoxins;
- uniformity of dosage units;
- particulate matter;
- antimicrobial effectiveness;
- impurities or related substances;
- other tests, as appropriate.

5.6 Additional information

▪ *Packaging and storage information*

For containers and container-closure system materials it is preferable to reference pharmacopoeial monographs, if available. The container system is chosen to prevent contamination and minimize degradation.

Storage conditions, which are necessary to assure the quality of the product until the BUD, should be included.

▪ *Labelling information*

Pharmacopoeial labelling requirements are not comprehensive, and only those statements that are necessary to demonstrate compliance with the monograph are mandatory. National and international requirements for licensed products may not apply to compounded preparations and specific guidance on compounded preparations should be available.

5.7 Stability information and beyond-use dating for compounded preparations

Where specified in a monograph, BUDs should be assigned conservatively, taking note of the following:

- the nature of the medicine and its degradation mechanism;
- the dosage form and its components;
- the method of sterilization, if applicable;
- the potential for microbial proliferation in the preparation;
- the container in which it is packaged;
- the expected storage conditions;
- the intended duration of therapy.

When an authorized or licensed product is used as the source of the API for a compounded preparation, the compounder should refer to the manufacturer for stability information and to the literature for information on stability,

compatibility and degradation of ingredients as well as using his or her compounding education and experience.

Compounded preparations should be stored under conditions that prevent contamination and minimize degradation. The chemical, physical and microbiological stability until the BUD should be assured.

▪ *Additional considerations*

For compounded preparations it is preferable to include a BUD based on laboratory-derived stability data in the pharmacopoeial monograph.

Susceptible preparations should contain suitable antimicrobial agents to protect against bacteria, yeast and mould contamination inadvertently introduced during or after the compounding process. When antimicrobial preservatives are contraindicated in susceptible compounded preparations intended for multiple use, storage of the preparation in a refrigerator is necessary and this should be stated in the monograph. Appropriate patient instruction and consultation is essential to ensure proper storage and handling of such compounded preparations by the patient or caregiver.

For sterile compounded preparations, it is preferable to include laboratory-derived stability and sterility information in pharmacopoeial monographs for such preparations. The laboratory-derived sterility information should evaluate the suitability of the sterilization method (for example, filtration, steam or dry heat) and container-closure integrity.

