European pharmacopoeia: Quality standards for medicines

Introduction

The word pharmacopoeia originates from Greek, *φαρμακοποιΐα*. Literally, the word means ‘medicine making’, and it refers to a type of book containing recipes for various medicines. Books like this have been used since ancient times.

In the past, the purpose of pharmacopoeias was to ensure that medicines were of good quality. The books contained individual formulas for medicines, including:

- The composition of the medicine – what it contained
- The preparation method – how to make the medicine
- The price of the medicine (in many cases)

Pharmacopoeias today

The basic purpose of a pharmacopoeia remains the same today: to ensure that medicines are of good quality. Medicines are no longer produced in pharmacies, and almost all medicines in developed countries are industrially produced. Therefore, the recipes of medicines are no longer listed in any pharmacopoeia. Instead, the essential elements of a modern pharmacopoeia such as the European Pharmacopoeia (Ph. Eur.) are the following:

- Quality standards for active substances
- General standards for dosage forms
- General standards for manufacture of medicines
- Monographs on finished products (only a few)

- Standard terminology

History of the European Pharmacopoeia

Historically, all countries in Europe produced and maintained their own national pharmacopoeias. After World War II, however, a new trend of internationalised pharmacopoeias emerged. Groups of countries began working together to replace their national pharmacopoeias with common ones – such as the European Pharmacopoeia. Other regions also retain their own common pharmacopoeias (for instance the United States Pharmacopoeia, USP).

Since 1952, the World Health Organisation (WHO) has published the International Pharmacopoeia. Initially, it included all medicines available and sold globally. Now, the International Pharmacopoeia focuses on:

- The WHO list of essential medicines
- Priority medicines of major public-health importance

Content of the European Pharmacopoeia

The European Pharmacopoeia contains a series of general monographs for the manufacturing of medicines, general methods of analysis of substances and medicines, and some general requirements for dosage forms (tablets, capsules, injections, etc.). The methods of analysis may also be used by the pharmaceutical industry for substances and medicines not described in the pharmacopoeia.

The bulk of the Ph. Eur. is made up of quality standards, which are noted both in the monographs and general methods sections. Quality standards contain analytical methods to

identify the substance and evaluate its quality and quantitative strength. Perhaps the most essential part of a quality standard of an active substance is the section on impurities.

Active substances of medicines are pharmacologically active due to the structure of the chemical molecule. No substance can be 100% pure, and impurities may come from:

- The manufacturing method – how a substance is produced or synthesised
- Degradation of the active substance – in other words, if it breaks down

Such impurities may have a chemical structure more or less similar to the active substance itself. They may also be pharmacologically active – either in a similar way to the active substance, or in a different way. Impurities may have an unwanted effect; for example, they may be toxic.

Some impurities will have been present at the time when the originator company tested the substance for effectiveness and safety. This means they have been part of the clinical and toxicological trials together with the active substance. Therefore, their presence at that level is acceptable. The monograph lists precisely all the impurities that can be detected by the method and defines the acceptable level of each of them.

If the method of synthesis is changed, or if another company produces the same substance after the patent expires, problems may arise. It is important to evaluate what implications these changes could have on the quality of the manufactured product. In particular, the following questions should be considered:

- Could new impurities appear?
- If yes, could the methods in the monograph detect them?
- What would an acceptable level be?

The company producing the substance may need to submit documentation for the suitability of the Ph. Eur. monograph to the regulatory authorities when applying for approval of a new medicine or when changing an existing medicine containing that substance.

The role of the European Directorate for the Quality of Medicines and Healthcare

The European Directorate for the Quality of Medicines and Healthcare (EDQM) and the European Pharmacopoeia Commission are bodies of the Council of Europe. The European Pharmacopoeia has a legal status in the EU and is acknowledged in the EU directives as establishing the official quality standards of the EU. The EDQM houses the European Pharmacopoeia Commission. The Commission is responsible for the work on monographs and general chapters of the pharmacopoeia. The practical work is performed by a number of expert groups.

The EDQM has established a concept named Certificate of Suitability (CEP). A manufacturer of an active substance may apply to the EDQM for such a certificate. The application should contain a full description of the chemical synthesis of the substance, and any potential and actual impurities should also be included. If the manufacturer can show that the quality of a substance is regulated by the Ph. Eur. monograph, the EDQM will grant a CEP.

The CEP is included in the dossier for the Marketing Authorisation Application (MAA). The regulatory authorities will accept the CEP as sufficient documentation that the Ph. Eur. monograph is fully capable of controlling the quality of the active substance.

The EDQM also has a role in the analytical control of medicines on the European market. A network of Official Medicinal Control Laboratories (OMCL) is coordinated by the EDQM in Strasbourg. The OMCL are responsible for performing analytical controls of medicines on their markets.

References

https://www.edqm.eu/en/european-pharmacopoeia-ph-eur-10th-edition

https://www.edqm.eu/

A2-5.17-v1.1