THE EUROPEAN PHARMACOPOEIA: ENSURING THE SAFETY AND GOOD QUALITY OF MEDICINES

The origins of the European Pharmacopoeia

The basic purpose of a pharmacopoeia (from the Greek word *φαρμακοποιΐα*, which literally means "medicine-making") is to ensure that medicines are safe and of good quality. Historically, medicines were produced in community pharmacies, but today almost all medicines in developed countries are industrially produced.

In the past, all European countries produced and maintained their own national pharmacopoeias. But after World War II, as the countries of Europe looked for new ways to co-operate, groups of countries began working together to replace their national pharmacopoeias with common ones.

In 1964, the Council of Europe adopted an international treaty, the *Convention on the Elaboration of a European Pharmacopoeia*, which provided the legal basis for the elaboration and implementation of the European Pharmacopoeia (Ph. Eur.) across the continent.

In the beginning, a group of eight countries were involved in this work. Today, 38 European countries plus the European Union (EU) as such collaborate, coordinate their efforts and take the necessary measures to implement the Ph. Eur. in their own territories. The Ph. Eur. also has legal status in the European Union and is acknowledged in the pharmaceutical legislation of the EU as establishing the official quality standards of the EU.

Published and regularly updated in English and French, the two official languages of the Council of Europe, it is a single reference work for official European quality standards and helps define the requirements to obtain a marketing authorisation of a medicinal product in Europe. Ph. Eur. quality standards apply throughout the entire life cycle of a product.

They are legally binding – as expressly laid down in the Council of Europe's *Convention on the elaboration of a European Pharmacopoeia* and in EU pharmaceutical legislation – and become mandatory on the same date in all 38[1] member states of the Convention.

The Ph. Eur.'s legally binding character and quality control methods ensure that everyone has access to good quality medicines. From a simple tablet taken with a glass of water to the most complex types of treatments, all medicines on the European market must comply with strict specifications on their composition, manufacturing processes and quality. This means that someone can buy a medicine (such as paracetamol tablets) in a pharmacy in any European country and obtain the same quality, regardless of the brand or type of medicine (original product or generic).

The role of the Ph. Eur. Commission in the quality control of medicines

The European Pharmacopoeia (Ph. Eur.) Commission is the governing body of the European Pharmacopoeia, responsible for overseeing the practical work of 800 or so experts in every field of the pharmaceutical sciences – all volunteers – who participate in currently 59 groups of experts and working parties.

[1] As of 26/07/2018

The Ph. Eur. Commission adopts all the texts to be published in the Ph. Eur. and takes technical decisions by consensus.

In addition the Commission evaluates proposals for inclusion, revision or suppression of monographs and general chapters, allocates agreed work items to a Group of Experts or Working Party, reviews overall progress made on the work programme, including revision work, on a yearly basis, and approves the terms of reference of Groups of Experts and Working Parties, defines criteria to be applied for the selection of experts and ad hoc specialists and appoints them.

Ph. Eur. texts are elaborated and updated by the groups of experts and working parties who meet several times per year in Strasbourg.

The European Directorate for the Quality of Medicines and HealthCare (EDQM) of the Council of Europe provides the scientific secretariat and logistical support for the work of the Ph. Eur. Commission, and facilitates the activities of its groups of experts and working parties.

The content of the Ph. Eur.

The Ph. Eur. contains almost 3,000 texts (also named as “monograph”), covering all therapeutic areas and consisting of:

- individual texts describing legally-binding quality standards for substances used in the manufacture of medicines or medicine ingredients (including active pharmaceutical ingredients, excipients, herbals, etc.);
- individual texts describing legally-binding quality standards for finished products;
- general monographs describing legally-binding quality standards for classes of substances (such as fermentation products or substances for pharmaceutical use) or for the dosage forms that medicines can take (tablets, capsules, injections, etc.); and
- general methods of analysis of substances used in the manufacture of medicines, which are not legally-binding and may also be used for substances and medicines not described in the Ph. Eur.

Ph. Eur. texts contain detailed analytical methods to identify the substance or product and control its quality and quantitative strength.

Ph. Eur. texts also address the issue of impurities in medicinal products, which do not offer any therapeutic benefit for the patient and sometimes are potentially toxic. Impurities are present at every stage of the manufacture of medicines: in starting materials, active pharmaceutical ingredients (APIs), reagents, intermediates, excipients and primary packaging materials. But the Ph. Eur. texts’s section on impurities is perhaps the most essential part of a quality standard of an active substance.

Active pharmaceutical ingredients 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, i.e. how a substance is produced or synthesised, or
- degradation of the substance – in other words, if it breaks down.

Impurities may also be pharmacologically active – either in a similar way to the active substance, or in a different way.

A number of impurities are present at the time when a company tests the substance for safety and efficacy in the course of developing a new medicine. This means they have been part of the toxicological and clinical trials together with the active substance. Therefore, their presence at that level has been assessed as safe and is hence acceptable.

The Ph. Eur. lists for each substance precisely all the impurities that can be detected by the test method prescribed in the monograph and defines the acceptable level of each of them. In addition, it contains a general monograph "Substances for pharmaceutical use" which defines further requirements for the control of impurities in active pharmaceutical ingredients and excipients, regardless of whether they are covered by an individual monograph in the Ph. Eur. or not.

If the method of synthesis is changed, or if another company produces the same substance after the patent expires, different or additional impurities 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?

  For example, there are different possible synthetic ways to produce valsartan, and for a same synthetic route different solvents and reagents may be used. The formation of impurities is linked to specific reaction conditions, specific synthetic ways. With a change to a route of synthesis new impurities can appear.

- If yes, could the methods in the monograph detect them?

  Analytical methods are only capable to control what they have been designed for. Consequently, any company intending to market a new medicine containing an API covered by a monograph in the Ph. Eur. or intending to modify the route of synthesis of such an API contained in an authorised medicine needs to submit a respective application to the regulatory authorities for approval, demonstrating that the relevant Ph. Eur. text(s) adequately control the substance's quality and impurity profile. In this context it may be necessary for the company to develop additional tests and propose respective limits for the control of new impurities which are currently not controlled by the Ph. Eur. text(s).

  The EU pharmaceutical legislation foresees a "feed-back" mechanism for such situations by obliging the respective regulatory authority assessing the documentation to inform the EDQM of the need for additional impurity controls and the company to provide respective data. This will then trigger a request for revision of the Ph. Eur. text. In addition, there may be other circumstances which require Ph. Eur. texts to be revised, e.g. in the context of changes to the regulatory environment, for example the EU REACH regulation, or to take account of new technologies. Hence, pharmacopoeial texts are routinely revised as the need arises.

- What would an acceptable level for an impurity be?

  Acceptable levels for an impurity are indicated in the Ph. Eur. and are defined based on safety evaluations performed by toxicological experts of the competent authorities. In addition, there are a number of internationally harmonised guidelines elaborated by toxicologists, which define acceptable levels of specific impurities, e.g. residual solvents or elemental impurities.