Procedure 4 (P4)

Everything you always wanted to know

1. Which substances/medicinal products are eligible?

Active substances or excipients present in medicinal products that are either still under patent OR single source are eligible for P4 elaboration, provided that the **medicinal product has been approved in at least one member state of the Convention on the Elaboration of a European Pharmacopoeia**. The corresponding medicinal products are also eligible for P4 elaboration.

2. How to propose a monograph for P4 elaboration

You can either contact the EDQM directly through our HelpDesk or make a proposal through a National Pharmacopoeia Authority (NPA) if your company is based in a member state that is a signatory to the European Pharmacopoeia Convention. Please provide the following information when making a proposal for P4 elaboration:

- the nature of the substance and its therapeutic use;
- the date of the first approval in Europe;
- the date of patent expiry;
- any additional data exclusivity or Supplementary Protection Certificate (SPC), if applicable.

What happens next?

The European Pharmacopoeia (Ph. Eur.) Department (EPD) will prepare an enquiry with the above information, which is sent to the NPAs to request approval for addition to the Ph. Eur. work programme. Once all feedback from NPAs has been gathered, the proposal is then submitted to the Ph. Eur. Commission who will endorse (or not) the decision to add this item on the Ph. Eur. work programme. See also the information provided in *6. What are the different steps/timelines?*

How long does this take?

The Ph. Eur. Commission meets three times per year: usually at the end of March, June and November. The enquiry takes a minimum of three weeks, so if you send your proposal at the beginning of February, May or October, the monograph might be added to the Ph. Eur. work programme within two months.

3. When is the best time to make a proposal?

As soon as possible after the first marketing authorisation.

Why so early?

Once eight years have passed since the first marketing authorisation (MA) has been granted, generic pharmaceutical companies are able to apply for MAs for generic versions. As soon as they have an MA, their specifications (different impurity profile, different limits, etc.) must be taken into account in the monograph, even if the product is not yet on the market. We have experienced on several occasions that MA had already been granted for medicinal products with great potential for generic manufacturing at *Pharmeuropa* stage, despite patent protection still being valid for few other years.

If the request for P4 elaboration comes only after 5 years, the time it takes for the draft monograph to be elaborated, verified generally in two independent laboratories (EDQM and an Official Medicines

Control laboratory – OMCL) and published in *Pharmeuropa* (see *6. What are the different steps/timelines?*) could mean that generic pharmaceutical companies are already in play. Should that happen, P4 monograph elaboration would no longer be possible: it will have to go to a classical expert group through procedure 1 instead, which means you lose all the advantages of the P4 elaboration (see *8. What are the advantages of P4 monograph elaboration?*).

4. What information/samples will be requested?

I. Data

1. Analytical procedures for the substance/medicinal product together with corresponding ICH-compatible validation data.
2. Current approved analytical specifications for all grades and strengths.
3. Rationale and justification for the choice of specifications (e.g. justification for choice of test procedures, batch data to support the proposed acceptance criteria).
4. Impurities and degradation products covered by the specification and a statement on whether the impurities and degradation products are qualified.
5. Results of the stability tests on the active substance/medicinal product in order to establish the storage section of the monograph and to define appropriate storage conditions for future chemical reference substances (CRS).

II. Samples

Note: the quantities indicated below apply to chemically defined active substances and corresponding medicinal products. For biotherapeutics, the quantities are defined on a case-by-case basis.

1. Samples (about 20 g) of at least 2, preferably 3, current production batches.
2. For medicinal products: samples (about 200 tablets/capsules or sufficient quantity to carry out all tests 5 times) of at least 2, preferably 3, current production batches of all available strengths and placebo samples (about 20 tablets/capsules) or excipient mixture (about 5 g).
3. Small samples (50-100 mg) of known impurities and/or related substances.
4. Sufficient quantities of any material (active substance, impurities, spiked material) indicated for use as a CRS in the procedures. A quantity equal to 2000 times the amount needed to carry out the tests involving the reference substance is considered sufficient. Usually 150-200 g of the active substance if used for LC assays (100 g otherwise) and 5-10 g of an impurity are needed to establish a CRS and provide a sufficient number of CRS units (for more information, see the enclosed Annex related to CRSs required for impurities). It is essential that batches of reference materials be made available during the elaboration of the monograph to ensure the efficient use of EDQM resources.
5. Certificates of analysis and safety data sheets for <u>all</u> the samples provided.
6. When monographs on the active substance and medicinal product(s) are elaborated in parallel, some of the samples/future CRSs may be of common use.

5. How is confidentiality ensured?

Confidentiality is a key consideration when appointing members of the Group of Experts P4.[1] Therefore, membership is restricted to members of licensing authorities, NPAs, OMCLs and EDQM staff. This differs from the classical expert groups of procedure 1, where members from academia and industry may also be present.

[1] 'Group of Experts P4' means both the Group of Experts P4 and the P4Bio Working Party.

Data is kept in a restricted folder only accessible to the concerned EDQM staff members and the experts involved in the elaboration and verification work.

6. What are the different steps/timelines?

The steps involved are the same as for any monograph published in the Ph. Eur. and are summarised in this diagram.

1. Addition to the Ph. Eur. work programme: this takes 2-4 months depending on the date the request is received (for more information, see *2. How to submit a monograph for P4 elaboration*).
2. A letter requesting data and samples is sent to the innovator once the Ph. Eur. Commission has agreed to add the monograph to the work programme (for more information, see *4. What information/samples will be requested?*).

   The sooner the innovator is able to provide the requested information, the sooner the monograph will be elaborated.
   Our current record for P4 monograph elaboration is for *Capecitabine*: it took only 18 months from receiving the data package and samples (October 2011) to adoption by the Ph. Eur. Commission (March 2013) of the text to be included in the Ph. Eur.
3. Draft monograph:

   Based on the data package, EPD prepares a draft monograph (if appropriate), taking into account the approved specifications (analytical procedures and acceptance criteria), the Technical Guide for the Elaboration of Monographs and other relevant technical guides, as well as the Style Guide (see *9. Useful links*). This takes usually 1-2 months. Exchanges with the innovator may take place to clarify outstanding points/request additional information.

   The draft monograph is shared with the innovator and may include a list of comments and questions which require additional information/explanation/clarification/justification. The draft is also shared with the Group of Experts P4. A rapporteur and co-rapporteur(s) are appointed, and they will be responsible for the review of the data package together with the EDQM, for monograph verification in their laboratories and for preparing a discussion paper on the comments received after the draft is published in *Pharmeuropa* (see below). For active substances, the EDQM Laboratory always acts as co-rapporteur. Once the comments and questions have been resolved, an updated draft is prepared, and this forms the basis for the experimental verification.
4. Experimental verification:

   The analytical procedures described in the draft monograph are checked, usually consecutively, in at least 2 different independent laboratories. For chemically defined active substances, as the EDQM Laboratory acts as co-rapporteur and performs the monograph verification together with the CRS establishment work, it can only perform the study when all the candidate CRSs are available in sufficient quantities. For biotherapeutics, experimental verification may be performed in parallel in more than two laboratories, in order to address the complexity of analytical procedures to be included in the monograph.

7. Can medicinal product monographs be elaborated in parallel?

Yes, absolutely. It is important to remember that, since the medicinal product monograph refers to the active substance monograph in its definition, adoption is only possible once the active

substance monograph has been adopted. However, both monographs can be adopted during the same session of the Ph. Eur. Commission.

Please note that a monograph cannot be elaborated for a medicinal product if the corresponding active substance is not already on the Ph. Eur. work programme or covered by a monograph published in the Ph. Eur.

8. What are the advantages of P4 monograph elaboration?

8.1. Direct contact with the EDQM

By using P4, provided the substance/medicinal product meets the corresponding criteria for monograph elaboration (see *1. Which substances/medicinal products are eligible?)*, you benefit from direct access to a dedicated member of EPD, who will be your single point of contact throughout the whole process.

You can contact this person by e-mail, by phone or even by teleconference if the items that you wish to discuss involve several people in your company. These meetings are usually very fruitful as they promote a mutual understanding of respective needs (Innovator/Ph. Eur.) and help clarify the requests made by EPD during elaboration.

8.2. Regular updates during the elaboration process/full transparency

Another big advantage of P4 is its full transparency: you can follow your proposal through all the steps of the monograph elaboration process. Usually we will prepare the first draft as soon as we receive the data package, together with a list of questions/points for clarification, related to the analytical procedures, the limits and/or the intended reference standards.

You will receive a copy of the draft monograph at each stage of the process: when it is ready for experimental verification, before publication in *Pharmeuropa* for public comment (ANP draft), before presentation to the Ph. Eur. Commission for adoption (COM draft) and after adoption.

We will send a summary of the outcome of the laboratory verifications of the monograph. You will have the opportunity to provide comments at each step if there is anything that does not seem correct or if you do not agree with something: we will only proceed once we have reached consensus.

8.3. Keep approved specifications unchanged

The Ph. Eur. principle is to keep the specifications as approved by the licensing authorities unchanged so that the monograph that will be included in the Ph. Eur. reflects what has been approved.

Unfortunately, this might not always be possible. For example, we may need to propose changes to one or more of the procedures described.

Typically, this happens when a toxic reagent (according to REACH Annex XIV or ICH Class 2 solvent) is described in a procedure. For instance, if hexane (Class 2 solvent) is used in the mobile phase, we will suggest replacing it with heptane (Class 3 solvent). In our experience, this change does not usually have any impact on the chromatography. The same is true of chloroform, which can no longer be used in the elaboration of new monographs.

In cases where proprietary reagents are described in a procedure, this may require development and validation of a modified analytical procedure.

We may also propose alternative or additional system suitability criteria or a different quantification method (using a dilution of the test solution instead of a solution containing the CRS) to ensure compliance with our Technical Guide for the elaboration of monographs (*9. Useful links*).

As regards acceptance criteria, please be aware that in Ph. Eur. monographs, specified impurities must always be identified by means of a CRS (either the pure impurity or a sample of the active substance containing the impurity). Identification by means of relative retention is NOT acceptable as we have seen on several occasions that this is not a reliable peak identification method and may result in incorrect peak assignment. Therefore, tighter acceptance criteria than those initially approved might be proposed.

For example, if an impurity X was specified with a defined limit (e.g. 0.15%) at the time of marketing authorisation and is no longer present or at very low levels in normal production batches, it can often be very difficult or even impossible to obtain the required CRS to unambiguously identify this impurity. In such cases, and, of course, if supported by your batch/stability data, we will suggest classifying impurity X as unspecified and thus controlled by the limit applying to unspecified impurities.

Rest assured that all changes will be submitted for your review before they are included in the draft monograph.

8.4. Possibility to request a CEP immediately after adoption

You can request a Certificate of Suitability (CEP) as soon as the monograph on an API is adopted. This can be very helpful when applying for marketing authorisation in countries that recognise CEPs (all Ph. Eur. member states, including those of the European Union plus other countries like Canada, Australia, New Zealand, Israel, Singapore, Tunisia and Morocco).

9. Useful links

For more information of our procedures for monograph elaboration, please refer to Annex 3 of Guide for the Work of the European Pharmacopoeia.

Technical Guide for the elaboration of monographs

Technical Guide for the elaboration of monographs on medicinal products containing chemically defined active substances

Technical guide for the elaboration of monographs on synthetic peptides and recombinant DNA proteins

Style Guide

ANNEX

Additional information regarding CRSs required for impurities

The following information should be supplied for the impurities covered by the specifications:

1. nature of the impurity: starting material, synthesis by-product, degradation product, etc.;
2. statement on its qualification (impurity reporting overview on impurity profile);
3. values for response or correction factors compared to the parent substance.

It is important to distinguish between:

1. impurities that occur in current production batches (give batch results + stability data under long-term storage conditions);
2. potential impurities that are detectable but no longer occur.

Normally only the impurities present above the identification threshold and those that have a high correction factor need to be listed as specified impurities.

Specified impurities require peak identification by means of:

1. individual impurity CRS: this is the preferred option in case of a large difference in response compared with the active substance (correction factor of the impurity ≤0.2 or ≥5);
2. spiked or 'dirty' batch;
3. in situ degradation reactions;
4. other approaches like different detection wavelengths, etc.

In order to help us define our strategy for CRS establishment, we kindly ask you to indicate which impurities you would be able to provide at a later stage and, most importantly, in which amount.

As a rule of thumb, the amounts needed are as follows:

1. 5-10 g for external impurity standard or impurity used for system suitability;
2. 10-20 g of a spiked or 'dirty' batch + small amounts of the individual impurities present in the mixture (at least 20 mg);
3. about 500 mg for impurities to be used in mixtures prepared by EDQM.