

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.

It is kindly requested to provide certificates of analysis and safety data sheets for all samples, as well as any available information on the salt form of impurity samples.

A. Samples for monograph verification

1. Samples of 3 current production batches of the active substance.

Amount needed: about 20 g per sample.

2. Samples of 3 current production batches of all available strengths of the medicinal product.

Amount needed for tablets/capsules: at least 100 tablets/capsules

Amount needed for other medicinal products: a sufficient quantity to carry out all tests 5 times.

3. Individual samples of all known impurities, if available.

Amount needed: about 100 mg per sample.

Please note that additional information on impurities is given in Annex 1 below.

4. Placebo of the medicinal product.

Amount needed for tablets/capsules: about 20 tablets/capsules

Amount needed for other medicinal products: about 5 g of excipient mixture.

B. CRS candidate materials

The EDQM needs to secure sufficient quantities of material for the purposes of establishment and production of Ph. Eur. CRSs. For that reason, the EDQM would like to enter into a discussion with the innovator in order to exchange about their potential contribution to the elaboration of Ph. Eur. CRSs.

Please note that availability of CRS candidate materials at the elaboration stage is essential to progress the Ph. Eur. monograph and allow its swift publication in *Pharmeuropa*.

Typically, the following types of CRS are needed:

- a) CRS for identification and/or assay of the active substance;

- b) One or more CRSs for system suitability and peak identification purposes. The specific requirements of these candidate materials will depend on the requirements of the analytical procedure.
- c) Individual impurity CRSs for peak identification and/or quantitation purposes.

General guidance on the typical quantity and quality of materials required for establishment and production of Ph. Eur. CRSs is provided in Annex 2 below, for information.

Please note that the final CRS strategy and the exact quantity required will only be fixed after exchange with the innovator and once a draft monograph text has been agreed upon. As part of the CRS strategy determination, certain considerations may have to be made for the long-term availability of CRS candidate material.

The EDQM would be grateful if the innovator could provisionally indicate which CRS candidate materials they would be able to provide in the future.

Note: when monographs on the active substance and medicinal product(s) are elaborated in parallel, some of the samples and CRS candidate materials 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.

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

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

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 1 – Additional information regarding impurities

It is kindly requested to supply the following information 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,
3. Values for response or correction factor(s) compared to the active substance,
4. Any available information on the salt form of impurity samples.

It is important to distinguish between:

1. impurities that occur in current production batches (please provide 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 the impurities at or below the reporting threshold for which a correction factor is needed are listed as specified impurities.

Specified impurities or those used for system suitability require peak identification by means of:

1. an 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. a spiked or “dirty” batch,
3. *in situ* degradation reactions,
4. other approaches like different detection wavelengths, etc.

ANNEX 2 – Additional information regarding quantity and quality of CRS candidate materials

The information below is to be understood as general guidance on the typical quantity and quality of materials required for establishment and production of Ph. Eur. CRSs.

It is noted that requirements not only depend on the intended use of the CRS, but also on the expected demand for the CRS by users of the Ph. Eur. monograph.

Furthermore, the EDQM has to ensure that sufficient CRS material is available well into the future, and beyond the publication of the new or revised monograph.

The quantities referenced below are to be considered as a guide only, and listed in order to prepare for a more detailed exchange with the EDQM on CRS strategy and candidate materials.

Depending on the use of the CRS, different cases can be distinguished:

- 1. Active substance CRS, used only for identification of the active substance.**

Required quality: compliance with monograph.

Example of amount that is typically required: from 60 g to 100 g.

- 2. Active substance CRS, used for assay**

Required quality: compliance with monograph.

Example of amount that is typically required: from 250 g to 500 g.

Please note that for CRS candidate materials under heading 1 and/or 2 above, a current production batch may be provided.

If an active substance CRS is used for both identification and assay, the requirements of CRS candidate material under heading 2 apply.

3. One or more mixture CRSs containing the active substance and one or more impurities, used for system suitability and/or peak identification

Required quality for system suitability: the composition corresponds to the sample used for validation and/or routine application of the analytical procedure.

Required quality for peak identification: should typically contain at least 0.10 % of each impurity to be identified.

Example of amount that is typically required: from 30 g to 60 g per candidate material.

4. One or more individual impurity CRSs used for system suitability, peak identification and/or quantitation

Required quality: corresponding to the material used during routine application of the analytical procedure.

Example of amount that is typically required (if only used for system suitability and/or peak identification): from 30 g to 60 g per candidate material.

Example of amount that is typically required (if used for quantitation): from 50 g to 100 g per candidate material.

If the impurity can be easily obtained from suppliers of chemicals and reagents, it may be sufficient to inform the EDQM where the impurity can be procured.