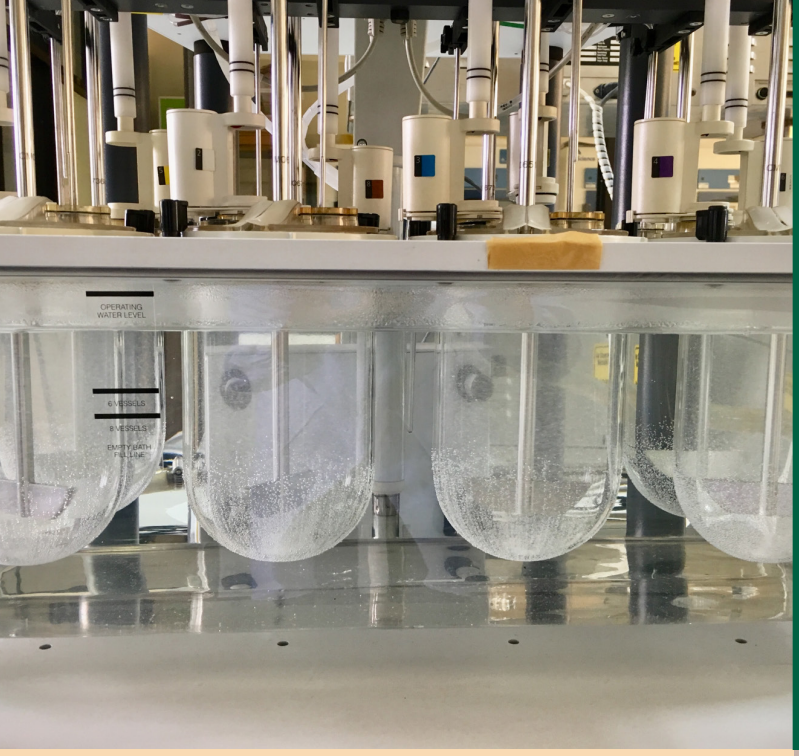

Technical Guide for the elaboration of monographs on MEDICINAL PRODUCTS CONTAINING CHEMICALLY DEFINED ACTIVE SUBSTANCES

European Pharmacopoeia

EDQM
2nd Edition
2022

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European Directorate for the Quality of Medicines & HealthCare | Direction européenne de la qualité du médicament & soins de santé

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

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1. INTRODUCTION

A monograph on a medicinal product is drafted with the same overall structure as a monograph on a chemically defined substance and the latest versions of both the *Technical guide for the elaboration of monographs* and the *Style guide for the European Pharmacopoeia (Ph. Eur.)* apply.

This Guide develops the specific points that are relevant to medicinal products containing chemically defined active substances and which are not presented in the above-mentioned overarching guides.

Monographs on radiopharmaceutical preparations are not within the scope of this guide.

Individual monographs on medicinal products shall be read in conjunction with Ph. Eur. chapter *1. General Notices*. Unless specifically exempted, the requirements of the relevant general monographs, for example, on dosage forms or *Pharmaceutical preparations (2619)*, apply to the individual monographs. For clarity, a reference to the relevant dosage form monograph is stated under Definition in the monograph.

2. GENERAL PRINCIPLES

Monographs are elaborated for medicinal products that have been authorised in at least one of the member states of the Ph. Eur. Convention and that contain a chemically defined active substance for which a monograph has already been published in the Ph. Eur. or is on the work programme of the Ph. Eur.

Monograph specifications are based on medicinal products currently approved in member states. Unless otherwise indicated, medicinal product monographs are intended for human use only and cover different formulations and strengths (where applicable) of the same dosage form, containing the same active substance.

Different forms (e.g. different solvates, salts and/or base/acid) are considered to be different active substances. As a result, separate medicinal product monographs are elaborated for each form (e.g. one for the product containing the salt form and one for the product containing the base/acid). In cases where different hydration forms of the active substance exist, these are covered in the same medicinal product monograph (e.g. water-free substance and monohydrate).

3. TITLE

The titles of monographs on medicinal products combine the appropriate active substance name and dosage form.

The International Nonproprietary Name (INN) (or an INN Modified (INNM) derived from it) should be used wherever it is available. If no INN or INNM exists, then a national non-proprietary name (e.g. British Approved Name (BAN)) or another appropriate, established name may be used. In cases where the active substance is a salt and/or a solvate (other than a

hydrate), the name of the salt and/or the solvate is stated in the monograph title but the hydration form is not.

The dosage form is derived from the appropriate dosage form monograph title or subtitle. If the monograph title states 'Tablets', it covers both immediate-release coated and uncoated tablets; if the title states 'Capsules', it covers both immediate-release hard and soft capsules. Otherwise, the appropriate subtitle of the dosage form monograph is used.

The Latin title of the monograph is based on the English title.

Examples of solid preparations intended for oral administration:

Raltegravir potassium tablets / chewable tablets
Deferasirox dispersible tablets
Active substance capsules

Example of liquid preparations intended for oral administration:

Deferiprone oral solution

Examples of parenteral preparations:

Fulvestrant injection
Lacosamide infusion
Active substance powder for injection or infusion
Active substance concentrate for injection or infusion

4. DEFINITION

The Definition section specifies the dosage form(s) covered by the medicinal product monograph, the scope (i.e. for human use) and refers to the relevant active substance monograph. Since one medicinal product monograph may cover one or several hydration forms, a reference is made to each relevant active substance monograph.

Examples of solid preparations:

Tablets containing *Sitagliptin phosphate monohydrate (2778)*, for human use.
Dispersible tablets containing *Deferasirox (2933)*, for human use.
Capsules containing *Active substance (XXXX)*, for human use.

Monographs whose Definition states 'tablets' cover uncoated and/or coated tablets, unless otherwise indicated. Monographs whose Definition states "capsules" cover hard and/or soft capsules, unless otherwise indicated.

If applicable, the Definition section specifies the exact dosage form(s) and states that the preparation is sterile.

Examples of parenteral preparations:

Sterile solution for infusion of *Lacosamide (2992)*, for human use. Sterile powder for solution for infusion of *Active substance (XXXX)*, for human use.

A cross-reference to the relevant dosage form monograph is included, for example:

They comply with the monograph Tablets (0478) and the following additional requirements.

5. PRODUCTION

For solvates other than hydrates, the following statement is published in the monograph:

PRODUCTION Manufacturers are expected to evaluate whether the presence of the active substance as a solvate is critical to the quality, efficacy and/or safety of the medicinal product and, where applicable, implement a control strategy for the corresponding solvent in the medicinal product, to the satisfaction of the competent authorities.

6. IDENTIFICATION

This section describes tests to confirm the identity of the active substance in the medicinal product in question. The tests described must make it possible to discriminate the active substance from compounds of a closely related structure that are likely to be present. It is not intended to assess the purity or determine the content of the active substance. Furthermore, no tests are included to control the presence of a specific counter-ion or determine the solvent/water content.

Examples of procedures of identification are listed below and detailed in paragraph II.4 of the *Technical guide for the elaboration of monographs*:

- Spectrophotometric analysis, such as recording of infrared spectra (IR);
- Chromatographic examination by means of liquid chromatography (LC);
- Ultraviolet and visible absorption spectrophotometry (UV-Vis).

Identification by a single chromatographic retention time is not regarded as being sufficiently specific. However, the use of two chromatographic procedures, where the separation is based on different principles or tests combined into a single procedure, such as LC/UV diode array, LC/MS or GC/MS, is acceptable.

For medicinal products, the preferred option to confirm the identity is to compare, with those obtained using a reference standard of the active substance (*active substance CRS)*:

- the retention time and the size of the principal peak obtained with the LC assay procedure, and
- the UV spectrum of the principal peak obtained with the LC assay procedure using a diode array detector. Whenever applicable, the UV spectrum should be recorded in the range of 210-400 nm.

However, if applicable, IR could also be used instead of the UV spectrum, either by direct measurement or following extraction; the latter procedure is more robust in view of the possible interaction of different excipients. To allow more flexibility, the two options (LC/UV diode array or LC + IR) may both be described in monographs on medicinal products.

In particular cases, for example where there is no characteristic chromophore, a TLC procedure can be prescribed instead of the comparison of the UV spectra.

7. TESTS

7.1 Related substances

In accordance with the ICH guidelines '*Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*' (ICH Q6A), '*Impurities in New Drug Products*' (ICH Q3B (R2)) and the EMA *Guideline on setting specifications for related impurities in antibiotics*, medicinal product monographs limit degradation products arising during the manufacture and shelf-life of the medicinal product, including those impurities of synthesis that are also degradation products.

In addition, for medicinal products containing a chiral active substance, control of the other enantiomer is considered necessary unless racemisation has been shown to be insignificant during manufacture and storage of the medicinal product. In cases where such control is needed, a test to confirm enantiomeric purity, preferably by chiral chromatography, is included in the monograph.

The most common and preferred procedure for control of organic impurities is liquid chromatography and the policy to be followed is described in the *Technical guide for the elaboration of monographs* and in the Ph. Eur. general chapters, such as *5.10. Control of impurities in substances for pharmaceutical use*. Whenever possible, the same procedure is described for the active substance and the corresponding medicinal product monograph(s).

In certain circumstances, it is necessary to identify impurities of synthesis in the medicinal product, for example, when they are detected in the test for related substances at a level greater than the reporting threshold in the medicinal product. Consequently, the monograph describes how to identify any such known impurities of synthesis (e.g. using existing reference standards described in the active substance monographs or a reagent), so that they are disregarded and are not taken into account.

Example:
- *reporting threshold:* 0.1 per cent, disregard the peak due to impurity A.

Medicinal product monographs are not designed to control impurities of synthesis that are not degradation products. However, tests provided in the monograph could be used to control impurities of synthesis known to be detected by the monograph, if further validated for that purpose by the user.

The quantification required for specified impurities, unspecified impurities and total impurities is preferably done using a dilution of the test solution, unless there is a large difference in the

detector response of an impurity (for more details see paragraph II.5.8.2.b 'Quantification' of the *Technical guide for the elaboration of monographs)*. Usually, a concentration corresponding to the limit set for the unspecified impurities is prescribed (e.g. 0.2 per cent). For the calculation of percentage contents, in contrast to the active substance monographs, the concentration of the active moiety (in the diluted solution) is usually taken into account.

7.2 pH

A test for pH is only included in monographs for liquid or semi-solid dosage forms when it is indicative of stability.

7.3 Water

A test for water is not included because the water content is specific to each product.

7.4 Solvates (excluding hydrates)

A test for the relevant solvent is not included but a Production section is included in monographs on medicinal products containing an active substance solvate (see item 5).

7.5 Other tests

Bacterial endotoxins, microbiology, sterility, uniformity of dosage units/content uniformity and residual solvent testing are already referenced and covered elsewhere in the Ph. Eur. (general chapters, general monographs, dosage form monographs, etc.).

They are only included in individual monographs if a specific procedure/sample preparation or a specific individual limit has to be described.

7.6 Dissolution / disintegration

Where appropriate, a dissolution or a disintegration test is described in medicinal product monographs. As stated in ICH Guideline Q6A and in line with the dosage form monographs, these tests are mainly applicable to solid forms such as tablets, capsules and granules but might also be appropriate for oral suspensions and dry powder products for suspension (e.g. in the case of insoluble substances).
A reference to one of the relevant general chapters is included, such as *Dissolution test for solid dosage forms (2.9.3), Dissolution test for patches (2.9.4), Dissolution test for medicated chewing gums (2.9.25), Dissolution test for lipophilic solid dosage forms (2.9.42) Disintegration of tablets and capsules (2.9.1), Disintegration test for solid rectal and vaginal dosage forms (2.9.2).*

The details of the scope of such a test and the conditions for its use in a marketing authorisation application are included in the *General Notices*.

When describing the dissolution test, mention must be made of the following parameters:

- *Type of apparatus*: apparatus 1 and 2 described in chapter *2.9.3* are commonly used;

- *Dissolution medium*: generally, an aqueous medium in physiological pH range is used and the volume is typically 900 to 1000 mL; the addition of surfactant should be avoided; if added, its concentration is kept as low as possible;
- *Rotation speed*: generally 50 r/min to 100 r/min;
- *Sinker devices:* used where necessary;
- *Time point(s)*: single-point measurements are usually considered to be suitable for immediate-release dosage forms. For modified-release dosage forms, appropriate sampling procedures are established;
- *Procedure used for quantitation*: LC and UV-Vis procedures are commonly used for the dissolution test.

When UV-Vis procedures are used, either the specific absorbance is given in the individual monograph or a reference standard with an assigned content is made available.
If the validated procedure prescribes, for example, a 1 mm cell and a 1 cm cell is used during the elaboration, consequently, a diluted solution is measured (in order to operate in the linear range of the instrument). The linearity of the procedure needs to be verified if the new concentration (diluted solution) is not covered by the linear range of the original procedure. In addition, the following information is indicated in the monograph:

Analysis. Ultraviolet and visible absorption spectrophotometry (*2.2.25*), using a path length of 1 mm. ….. When a different path length is used, the solutions may be diluted accordingly (e.g. for a path length of 1 cm, 10-fold dilution for 200 mg tablets).

When LC procedures are used, the individual monograph includes a repeatability criterion and, whenever necessary, a stoichiometric conversion factor is applied for calculation of the content (see under Assay).

As outlined in ICH Guideline Q6A, for rapidly dissolving medicinal products containing active substances that are highly soluble throughout the physiological range, a disintegration test may be substituted for a dissolution test.

8. ASSAY

Medicinal product monographs must include a specific, stability-indicating assay to determine the content. Whenever possible, the same procedure as that described for the related substances test is used. Results of content uniformity testing for medicinal products can also be used for quantitation of the content, if the procedure is appropriate for use as an assay.

The purpose of the assay is to determine whether the content of the active substance is within acceptable limits of the label claim and the limits are therefore stated in terms of the active moiety declared on the label. The standard limit for the content is usually 95.0 per cent to 105.0 per cent of the content stated on the label.

Preferably, at least 5 units of the medicinal product are used to prepare the test solution.

The criteria for the repeatability given in chapter *2.2.46. Chromatographic Separation Techniques* do not apply to medicinal products. Therefore, an individual criterion is introduced into each medicinal product monograph:

System suitability: reference solution (a).
- *repeatability:* maximum relative standard deviation of X per cent determined on 6 injections.

When the reference standard of the active substance is used for the determination of the content, a stoichiometric conversion factor may be necessary for the calculation. For example, the content limits in the monograph *Sitagliptin tablets* (2927) are expressed with reference to sitagliptin, while the assigned content of *sitagliptin phosphate monohydrate CRS* is expressed as a percentage *m/m* of sitagliptin phosphate. In such cases, the following information is given:

Calculate the percentage content of sitagliptin ($C_{16}H_{15}F_6N_5O$) taking into account the assigned content of *sitagliptin phosphate monohydrate CRS* and applying a conversion factor of 0.806.

A non-specific assay can also be applied provided that it is justified and that other supporting analytical procedures are used to achieve overall specificity, for example, a combination of a volumetric titration and a suitable selective test for impurities.

For medicinal products containing a chiral active substance, an achiral assay may be sufficient where racemisation has been shown to be insignificant during manufacture and storage of the medicinal product. Otherwise, a chiral assay should be used, or alternatively, the combination of an achiral assay together with a validated procedure to control the presence of the other enantiomer (test for enantiomeric purity) may be used.

9. STORAGE

Information regarding storage is given in the *General Notices*, in the general monograph *Pharmaceutical preparations (2619)* and may also be stated in the relevant dosage form monograph. Additional information is usually not provided in medicinal product monographs unless otherwise recommended by the group of experts and ultimately adopted by the Ph. Eur. Commission.

10. LABELLING

Information regarding labelling is given in the *General Notices*, in the general monograph *Pharmaceutical preparations (2619)* and might also be stated in the relevant dosage form monograph. Additional information is usually not provided in medicinal product monographs unless otherwise recommended by the group of experts and authorised by the Ph. Eur. Commission.

11. IMPURITIES

This section lists all the impurities, whatever their nature (degradants or synthetic), that are known to be detected by one or other of the tests in the monograph.

This increase in the transparency of pharmacopoeial specifications is of assistance to competent authorities, manufacturers and others when considering whether the standards in the monograph are appropriate for a new source. It is emphasised that such lists are not intended to be exclusive and other, unnamed impurities may also be controlled by the procedure(s).

Impurities already listed in the monograph on the active substance, designated by a capital letter (A, B, C, D, etc.), keep their name.

Impurities specific to the medicinal product are designated by "FP-" followed by a letter of the alphabet (FP-A, FP-B, etc.); this is to avoid confusion with impurities listed in the active substance monograph.

Example:

IMPURITIES

Specified impurities: A.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph.): *B, C, D, E, F, FP-A, FP-B, FP-C*.

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