

Draft for public consultation

European Commission guideline on aspects of the application of Article 8 of Regulation (EC) No. 141/2000¹:

Assessment of similarity and/or clinical superiority of orphan medicinal products when assessing marketing authorisation applications and variations

Paragraph 5 of Article 8 of Regulation (EC) No. 141/2000 requires the Commission to draw up detailed guidelines for the application of Article 8 of that regulation². This guideline fulfils part of that requirement, describing the procedures for application of Article 8 and specifically provides guidance for the assessment of similarity of medicinal products and the application of Article 8 paragraph 3. This guideline does not cover the application of Article 8 paragraph 2 of Regulation (EC) No. 141/2000 relating to the reduction of the period of market exclusivity.

This guideline should be read in conjunction with:

- Regulation (EC) No 141/2000 of the European Parliament and of the Council on orphan medicinal products,
- Commission Regulation (EC) No 847/2000 laying down the provisions for implementation of the criteria for designation of a medicinal product as an orphan medicinal product and definitions of the concepts “similar medicinal products” and “clinical superiority”.
- Communication from the Commission on Regulation (EC) No 141/2000 of the European Parliament and of the Council on orphan medicinal products (2003/C 178/02, 29 July 2003).

¹ Article 8 of Regulation (EC) No. 141/2000:

“Market exclusivity

1. Where a marketing authorisation in respect of an orphan medicinal product is granted pursuant to Regulation (EEC) No 2309/93 or where all the Member States have granted marketing authorisations in accordance with the procedures for mutual recognition laid down in Articles 7 and 7a of Directive 65/65/EEC or Article 9(4) of Council Directive 75/319/EEC of 20 May 1975 on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products (7), and without prejudice to intellectual property law or any other provision of Community law, the Community and the Member States shall not, for a period of 10 years, accept another application for a marketing authorisation, or grant a marketing authorisation or accept an application to extend an existing marketing authorisation, for the same therapeutic indication, in respect of a similar medicinal product.

(...)

3. By way of derogation from paragraph 1, and without prejudice to intellectual property law or any other provision of Community law, a marketing authorisation may be granted, for the same therapeutic indication, to a similar medicinal product if:

(a) the holder of the marketing authorisation for the original orphan medicinal product has given his consent to the second applicant, or

(b) the holder of the marketing authorisation for the original orphan medicinal product is unable to supply sufficient quantities of the medicinal product, or

(c) the second applicant can establish in the application that the second medicinal product, although similar to the orphan medicinal product already authorised, is safer, more effective or otherwise clinically superior.

(...)”

² Indent 5 of Article 8 of Regulation (EC) No. 141/2000 states: *“The Commission shall draw up detailed guidelines for the application of this Article in consultation with the Member states, the Agency and interested parties”*

TABLE OF CONTENTS

Introduction.....	3
I Procedural aspects.....	3
I.1 Principles	3
I.2 Information to be submitted by the applicant	4
I.3 Tracking of potential similarity issues.....	4
I.4 Procedures for assessing “similarity” or “clinical superiority”.....	5
I.4.1 MAA submitted for an (orphan) condition for which a product has obtained market exclusivity under Regulation 141/2000.....	6
I.4.1.1 MAA for the same orphan condition is submitted with acknowledgement of similarity with an authorised orphan medicinal product and justification for derogation.	6
I.4.1.2 MAA for the same orphan condition is submitted without acknowledgement of similarity/“application of Article 8.3, including clinical superiority”.....	6
I.4.2 Two MAAs for the same orphan condition are under assessment in parallel.	7
II General principles for CHMP assessment of similarity	9
II.1 Molecular structural features	9
II.2 Mechanism of action	10
II.3 Therapeutic indication	11
III Processing of other derogations.....	11
IV Assessment of “clinical superiority”	12
V Glossary of the abbreviations used	13
Appendix 1:.....	14
Examples to illustrate cases: ‘structural similarity’ of macromolecules.....	14
Appendix 2:.....	16
Examples to illustrate cases: ‘structural similarity’ of chemically-synthesised active substance	16

Introduction

According to Article 8 of Regulation (EC) No. 141/2000, where a marketing authorisation in respect of an orphan medicinal product is granted in all Member States, the Community and the Member States shall not, for a period of 10 years, accept another application for a marketing authorisation, or grant a marketing authorisation or accept an application to extend an existing marketing authorisation, for the same therapeutic indication, in respect of a similar medicinal product. Paragraph 3 of the same article describes three types of derogations, including the case where the second medicinal product would be safer, more effective or otherwise clinically superior (these three concepts are referred to as “clinical superiority” in this guideline).

For the purposes of the implementation of Article 8, the Commission Regulation (EC) No 847/2000 provides the following definitions:

- “similar medicinal product” means a medicinal product containing a similar active substance or substances as contained in a currently authorised orphan medicinal product, and which is intended for the same therapeutic indication.
- “Similar active substance” means an identical active substance, or an active substance with the same principal molecular structural features (but not necessarily all of the same molecular features) and which acts via the same mechanism. The Commission Regulation (EC) No 847/2000 then provides specific examples.
- “Active substance” means a substance with physiological or pharmacological activity.

In accordance with the Commission Communication on orphan Medicinal Products (2003/C 178/02, 29 July 2003) it is the responsibility of the CHMP to give an opinion on the similarity of two products and on whether or not they are intended for the same indication, for centralised marketing authorisation applications (MAA). For application filed through the Mutual Recognition Procedure (MRP), it is the responsibility of the National Competent Authority(ies) concerned.

It should be noted that it is the responsibility of the Committee for Orphan Medicinal Products (COMP) to conduct any review relating to the orphan designation criteria.

In this guideline, the term “relevant Competent Authority” refers either to the EMEA or a National Competent Authority depending on the type of marketing authorisation procedure (centralised or mutual recognition) utilised.

I Procedural aspects

I.1 Principles

In order to implement Article 8, a procedure has been set up to ensure that during the market exclusivity period of an orphan medicinal product, another marketing authorisation or an extension of an existing marketing authorisation for the same therapeutic indication, in respect of a similar medicinal product, will not be accepted or granted, unless the sponsor has established that one of the derogations listed in Article 8 applies.

Implementation therefore requires a procedure for tracking potential similarity issues, for assessing similarity and, where necessary, for assessing justification that one of the derogations (particularly in the case of Article 8.3(c) “clinical superiority”) applies.

In the case of two products being potentially similar, the applicant of the second product will have to provide appropriate documentation on its position regarding similarity and, if relevant, justification that a derogation applies. Such documentation should be submitted in Module 1.7 of the application for marketing authorisation.

The relevant Competent Authority will assess “similarity”/“clinical superiority”, in parallel with its evaluation of the quality/safety/efficacy of the medicinal product, before issuing a marketing authorisation.

For centralised procedures, the CHMP opinion on “similarity”/“clinical superiority” will be part of the same overall opinion on quality/safety/efficacy (QSE). The European Commission will proceed to

grant a marketing authorisation provided that the CHMP opinion includes positive recommendations on both QSE and “similarity”/“clinical superiority”.

I.2 Information to be submitted by the applicant

Information to address potential “similarity” and, where applicable, justify that one of the derogations laid down in Article 8.3, paragraphs (a) to (c) of the Regulation 141/2000 applies should be submitted in module 1.7 of the application for marketing authorisation.

For **similarity**, a report should be included in module 1.7.1 comparing the two products in the context of similarity as defined in Art. 3.3 of Regulation (EC) No 847/2000 and concluding on similarity or “non” similarity, with particular reference to

§ mechanism of action,

§ structural similarity.

To support that one of the derogations laid down in Article 8.3, paragraphs (a) to (c) of the same Regulation applies, the following information should be submitted in module 1.7.2, as applicable:

(a) the holder of the marketing authorisation for the original orphan medicinal product has given his **consent** to the second applicant,

A signed letter from the holder of authorised orphan medicinal product confirming his/her consent for the second applicant to file an application for marketing authorisation, in accordance with Art. 8.3 (a) of Regulation (EC) No 141/2000, should be provided.

(b) the holder of the marketing authorisation for the original orphan medicinal product is **unable to supply sufficient quantities** of the medicinal product, or

A report describing why supply of the authorised orphan medicinal product is deemed to be insufficient, in accordance with Art. 8.3 (b) of Regulation (EC) should be submitted.

The report should include details of the supply problem and an explanation of why as a result patients’ needs in the orphan indication are not being met. All claims should be substantiated by qualitative and quantitative references.

(c) the second applicant can establish in the application that the second medicinal product, although similar to the orphan medicinal product already authorised, is safer, more effective or otherwise **clinically superior**.

A critical report justifying why the medicinal product which is the scope of the application is deemed to be “clinically superior” to the authorised orphan medicinal product, in accordance with Art. 8.3 (c) of Regulation (EC) No 141/2000 should be submitted.

The report should include a comparison of the two products in the context of “clinical superiority” as defined in Art. 3.3(d) of Regulation (EC) No 847/2000, with particular reference to

§ the results of clinical studies,

§ the scientific literature.

I.3 Tracking of potential similarity issue

For any application for marketing authorisation (MAA) or variation to extend an indication, potential similarity with an authorised orphan medicinal product should be checked by the relevant Competent Authority prior to validating the application and issuing a marketing authorisation or granting a CHMP positive opinion, in the case of a centralised procedure.

At the time of validation, this check will be performed with reference to the application forms for marketing authorisation (see section 1.2 of the application form) or for variation (see section on type II variation).

Considerable time may elapse between validation of an application and adoption of an opinion/grant of a marketing authorisation, checking for potential “similarity” will, therefore, be repeated prior to the grant of the marketing authorisation, as another orphan medicinal product may have been authorised for the same condition in the meantime. The relevant Competent Authority will check at

validation stage of any MAA whether there is another MAA under evaluation for the same orphan condition.

Checking for potential similarity is to be performed with reference to the Community Register of orphan medicinal products for human use (<http://pharmacos.eudra.org/F2/register/orphreg.htm>, <http://pharmacos.eudra.org/F2/register/alforphreg.htm>), which provides information on the active substance and the authorised indications of orphan medicinal products.

I.4 Procedures for assessing “similarity” or “clinical superiority”

Following identification of a potential product similarity issue, the relevant Competent Authority will initiate the procedure for assessing “similarity” and, if appropriate assessing “clinical superiority”.

Centralised Procedure

Both procedures will be 60-day procedures that may be extended by 30 days (with clock-stop) where necessary. The start date may vary depending on the particular circumstances (see different scenarios described below) and may be prior to validation. The Rapporteur and CoRapporteur (nominated for the application) will prepare a joint report by day 30. CHMP members will comment on the reports by day 45. The CHMP Quality Working Party (QWP) or Biotechnology Working Party (BWP) will advise the CHMP on the structural part of the similarity assessment by day 60. At day 60, the CHMP will finalise the assessment report on “similarity” or “clinical superiority” or adopt a list of questions to be addressed by the applicant (clock stop). In the latter case, a Rapporteur/CoRapporteur’s revised joint assessment report will be submitted at day 75 (i.e 15 days after restarting the clock) and CHMP report will be finalised at day 90, following an oral explanation if necessary. The CHMP opinion on “similarity”/“clinical superiority” will be part of the CHMP Opinion on the application. The applicant may appeal the CHMP Opinion, provided that it notifies the EMEA in writing of its intention to appeal within 15 days of receipt of the Opinion.

In cases where “similarity”/“clinical superiority” are assessed versus an orphan medicinal product authorised through the MRP, the Mutual Recognition Facilitation Group (MRFG) will be informed at the start of the procedure and consulted at day 60 prior to finalising the CHMP assessment at day 90.

National procedures and Mutual Recognition Procedure

“Similarity” and “clinical superiority” issues will be assessed by the National Competent Authority (NCA) during the overall assessment of an application for marketing authorisation or for an extension of indication of a nationally authorised medicinal product authorised nationally or through Mutual Recognition Procedure (MRP).

The NCA will assess similarity on a national basis. However, it is highly recommended to seek advice from the QWP or the BWP, depending on the medicinal product concerned.

The assessment of the “clinical superiority” may be performed in conjunction with the CHMP or may be performed at the NCA level.

In the case of an application for an extension of indication of a medicinal product authorised through MRP, the Reference Member State (RMS) will inform Concerned Member States (CMS) of its conclusion in the preliminary assessment report circulated on Day 70 and CMS will have the opportunity to comment on the “similarity” and “clinical superiority” issues on Day 85. On Day 89, the RMS will finalise the assessment report on “similarity” and “clinical superiority” or will stop the clock of the procedure in order that the marketing authorisation holder may send responses to questions raised by Member States. In the latter case, a final assessment report will be circulated on Day 90 and the procedure will be closed on day 120.

In all cases, the EMEA should be informed of the conclusions.

In cases where “similarity”/“clinical superiority” are assessed versus an orphan medicinal product authorised through the Centralised Procedure, the National Competent Authority(ies) will inform the EMEA at the start of the procedure and consult the CHMP QWP or BWP for assessing similarity and the CHMP for assessing “clinical superiority” (30-day consultation period).

In practice, different scenarios can be envisaged and are further detailed in the following sub-sections. A tabulated overview of the procedures for the different scenarios described below (for centralised applications) is provided at the end of this section.

I.4.1 MAA submitted for an (orphan) condition for which a product has obtained market exclusivity under Regulation 141/2000

The second applicant should submit documentation on “similarity” and, where necessary, justification for any derogation at the time of the MAA submission. At the time the application is filed, the relevant Competent Authority will check that the appropriate documentation on “similarity” and “clinical superiority” has been submitted.

The relevant Competent Authority will only validate an application if information on the potential “similarity” has been submitted at the time of the MAA, and a report on clinical superiority (or justification for one of the other derogations in Article 8.3) has been submitted in cases of established similarity. The following situations may occur.

I.4.1.1 MAA for the same orphan condition is submitted with acknowledgement of similarity with an authorised orphan medicinal product and justification for derogation.

The relevant Competent Authority will confirm “similarity” and “clinical superiority” (or one of the other derogations in Article 8.3) in parallel to the assessment of QSE.

Centralised procedure

Assessment to confirm “similarity” will be started at the same time as the application procedure and finalised by day 90. In some cases, similarity with respect to therapeutic indications may need to be confirmed at the time of the CHMP Quality, Safety and Efficacy (QSE) opinion.

As the assessment of efficacy and safety may impact on the assessment of “clinical superiority”, the latter will be assessed between Day 121 and Day 180/210 of the application procedure, at the latest.

Before issuing a CHMP positive opinion at day 210, the EMEA will check whether other orphan medicinal product(s) have been authorised for the same condition. Where this is the case, the applicant will be asked to submit further relevant “similarity”/“clinical superiority” documentation and the procedural clock will be stopped to permit a parallel evaluation of “similarity”/“clinical superiority” by CHMP, according to the above-mentioned timelines. Should a new “similarity” issue be identified during the decision making process, the European Commission may refer the CHMP opinion back to the EMEA for further evaluation.

National procedures and Mutual Recognition Procedure

Once a first orphan medicinal product has market exclusivity, no further MA can be granted for a similar medicinal product in the same therapeutic indication: in particular, if on-going and/or repeat-use MR procedures are running and if marketing authorisations have not been granted in all Member States, it is important to specify that, from the date of the first orphan MA, no further authorisations can be granted in respect of a similar product in the same therapeutic indication. The repeat-use mutual recognition procedures cannot be undertaken or finalised.

If a national MAA for the same orphan condition is submitted with acknowledgement of similarity with an authorised orphan medicinal product and justification for a derogation, “similarity” and “clinical superiority” issues will be assessed by the NCA in the frame of the assessment of the application for marketing authorisation (see above section I.4). Where a potential similarity issue is detected for an application filed nationally (or through MRP), the National Competent Authority will inform the EMEA.

I.4.1.2 MAA for the same orphan condition is submitted without acknowledgement of similarity/“application of Article 8.3, including clinical superiority”.

If a relevant Competent Authority identifies a potential similarity issue, the applicant will be asked to complete the application with information on “similarity” and “clinical superiority” (or justification for one of the other derogations in Article 8.3), before the validation proceeds.

Where an applicant considers that the medicinal product which is subject of the MAA is not “similar” to an authorised orphan product, validation of the application will only proceed once the applicant has submitted a report justifying the lack of similarity for review by the relevant Competent Authority (see above-mentioned procedures).

- Where the relevant Competent Authority concludes that the product is not similar to an authorised orphan medicinal product, the application will be assessed according to the usual procedure.
- Should the relevant Competent Authority consider that there is similarity, a report on clinical superiority (or justification for one of the other derogations in Article 8.3) will be requested prior to validation of the application.

I.4.2 Two MAAs for the same orphan condition are under assessment in parallel.

Any potential similarity issue should have been identified by the Competent Authority during the validation of the second application.

In the exceptional case of two similar orphan medicinal products being granted Marketing Authorisations (in all Member States, if national) for the same orphan indication on the same dates, an opinion on similarity will not be necessary as the products will share market exclusivity.

Otherwise, as soon as one of the products with orphan status obtains a marketing authorisation, the relevant Competent Authority will inform the second applicant that a marketing authorisation for a potentially similar orphan product has been granted in the intended condition of their product. Reports on “similarity” and/or justification for one of the derogations in Article 8.3 will be requested from the second applicant.

Centralised procedure

Where possible, the applicant’s justifications will be submitted at day 121 of the marketing authorisation application and the CHMP assessment of “similarity”/“clinical superiority” will be performed in parallel to the finalisation of QSE assessment procedure. If this is not possible (e.g. similarity issue appears after day 121), in order to keep the 210-day legal timeframe, the clock of the QSE assessment procedure will be stopped (up to a maximum of 60/90 days) to assess “similarity” and finalise the assessment of “clinical superiority” at the same time as the QSE assessment.

National Procedure and Mutual Recognition Procedure

In the case where a medicinal product has been designated as an orphan product and its marketing authorisation is under assessment but has not been granted by the European Commission or by all Member States, yet:

- if a similar medicinal product not designated as an orphan medicinal product is under assessment by a National competent authority, the marketing authorisation may be granted and EMEA should be informed.
- If a similar medicinal product that has also been designated as an orphan medicinal product for the same orphan condition is under assessment by a National Competent Authority, the marketing authorisation may be granted. Nevertheless, the market exclusivity will be obtained only when this medicinal product will be authorised through mutual recognition procedure in all Member States of the European Union. This has to be completed before the first product.

If a medicinal product has been designated as an orphan medicinal product and a national application for a product with similar structural feature and mechanism of action is under assessment by the National Competent Authority in a different therapeutic indication, there is no obstacle to granting a marketing authorisation, as long as the decision is in accordance with the principles in legislation and set in this guideline. However, the EMEA should be informed.

TABULATED OVERVIEW OF THE PROCEDURES FOR DIFFERENT SCENARIOS (FOR CENTRALISED APPLICATIONS)				
Possible Scenario	MAA submitted with acknowledgement of similarity with authorised orphan medicinal product	MAA submitted without acknowledgement of similarity with authorised Orphan And EMEA identifies potential similarity issue	MAA under assessment when Orphan product authorised	
Validation	<ul style="list-style-type: none"> - Check all potential similarity issues have been identified in application form. - Check report on similarity submitted - Check report justifying derogation (c) submitted 	<ul style="list-style-type: none"> - MAA asked to complete application - If similarity recognised by applicant, see previous column - If similarity denied by the applicant, applicant has to submit report on similarity - CHMP assess similarity within 60/90 days prior to validation - In case of similarity, dossier validated only if derogation report submitted by applicant 	Similarity not relevant at the time of the validation	
			<ul style="list-style-type: none"> - Authorisation of the orphan product before day 121 of the ongoing application 	<ul style="list-style-type: none"> - Authorisation of the orphan product after day 121 of the ongoing application
Day 0-120	<ul style="list-style-type: none"> - CHMP to confirm similarity based on submitted report and liaison with QWP, BWP or MRFG as appropriate 	<ul style="list-style-type: none"> - CHMP to assess similarity based on submitted report and liaison with QWP, BWP or MRFG as appropriate 	<ul style="list-style-type: none"> - Second applicant informed and asked to submit reports on similarity and derogation (c) by Day 121 	
Clock stop				
Day 121-210	<ul style="list-style-type: none"> - CHMP to assess derogation (c) based on submitted report and QSE assessment as appropriate - Before CHMP opinion, EMEA to check no new similarity issue - Opinion sent to EC including QSE, similarity, derogation (c) 	<ul style="list-style-type: none"> - CHMP to assess derogation (c) based on submitted report and QSE assessment as appropriate - Before CHMP opinion, EMEA to check any new similarity issue - Opinion sent to EC including QSE, similarity, derogation (c) 	<ul style="list-style-type: none"> - CHMP assess similarity within 60/90 days - CHMP to assess derogation C based on submitted report and QSE assessment as appropriate - Before CHMP opinion, EMEA to check any new similarity issue - Opinion sent to EC including QSE, similarity, derogation (c) 	<ul style="list-style-type: none"> - Second applicant informed and asked to submit reports on similarity and derogation (c) by Day 210 - Clock stop to a maximum of 60/90 days to allow assessment of similarity and derogation C, by 210 of QSE assessment.
Decision Making phase	<ul style="list-style-type: none"> - EMEA to follow-up for new similarity issues - In case new similarity issue appears, EMEA to inform EC who will send back the opinion to CHMP - EC to issue decision as appropriate 			

II General principles for CHMP assessment of similarity

Article 3 of Commission Regulation (EC) No 847/2000 defines similar active substance as “an identical active substance or an active substance with the same principle molecular structural features (but not necessarily all of the same molecular structural features) and which acts via the same mechanism”. Therefore, the similarity assessment will take into consideration molecular structural features, mechanism of action and therapeutic indication. The following sections provide guidance for assessment of similarity as defined in Article 3 of Commission Regulation (EC) No 847/2000.

In assessing similarity, consideration will be given to International Non proprietary Names (INN). The International Non proprietary Names (INN) may provide preliminary information in assessing the similarity of the mechanism of action and structural features. In the INN system, the names of pharmacologically-related substances may show their relationship by using a common "suffix"/substem.

II.1 Molecular structural feature

Indent 3. (c) of Article 3 of Commission Regulation EC No. 847/2000 defines “similar active substance” and provides specific considerations for macromolecules and radiopharmaceutical active substances.

General considerations

The applicant should provide a reasoned argument to support their claim that the two products are not similar, as part of the information provided in module 1.7. The general considerations given below should be taken into account, though for macromolecules particularly complex biological medicinal products, not all of these considerations may be appropriate.

Satisfactory information should be provided by the applicant to confirm the proposed structure of the molecule, i.e. the proof of structure should be acceptable:

- all the evidence relating to proof of structure should be summarised in unambiguous two- and three dimensional graphical representations, where possible;
- where possible, the active substance should be described precisely using systematic terminology, e.g. IUPAC or CAS nomenclature;
- where the active substances have a recommended INN name, the WHO structures and reports should be provided;
- If any of the above information is not provided or not available, justification should be given.

A critical judgement will be made on all the information provided by concerned applicant(s), together with any information concerning structure published by the WHO relating to the INN, if there is one.

It should be kept in mind that certain observed differences in structure may appear to be major if the molecules are considered only in the crystalline state (i.e. based on X-Ray data), where the positions of the atoms are restricted within narrow limits depending on the crystalline form. However, in solution, the molecules are not so rigidly disposed, due to free rotation around the C-C single bonds for example, and this could have the effect of ‘smoothing’ these apparent differences and rendering them not so large as they may appear to be in the crystalline state. Since molecules exert their biological action in solution, major structural differences seen in the crystalline state may not be relevant to judgements of similarity.

It should be noted that software programs are available for the electronic generation and archiving of molecular structures, and many of them allow ‘similarity searching’ to identify molecules having common or similar molecular architectural features (2- or 3- dimensional). Some utilise a binary matching process based on the presence or absence of sub-structure elements (fingerprints), others base similarity on overall 3-D geometry, nearest-neighbour-distance, electron density mapping etc. Such inexact or fuzzy structure matching is particularly valuable to the pharmaceutical industry in searching for lead compounds. Since the 1970’s, developments in chemometrics, information science, computational chemistry, taxonomy, etc. have converged on the issue of similarity such that a quantitative measure of the degree of structural similarity between molecules may be calculated.

For small molecules, quantitative measures of similarity such as the Tanimoto coefficient³ or the weighted Tversky index⁴ may be mentioned, among many others, each having their own dependencies, advantages and disadvantages.

However, the conceptual basis of similarity is constantly being refined and consolidated, and more improved and rigorous mathematical treatments are continually being developed and applied to molecular structures.

Relevant and validated algorithms could assist in detecting potential similarity cases, and could assist in the interpretation of similarity according to Article 3 (paragraphs (3)c, and 3(c) subparagraph 1) of Commission Regulation (EC) n° 847/2000).

Examples of structural similarity assessment:

Appendix 1: examples are given for macromolecules.

Appendix 2: examples are given for chemically-synthesised small molecules. It should be noted that the principles apply not only to chemically-synthesised active substances, but also to well-defined natural substances e.g. herbal substances, including mixtures of these substances. Any considerations of ‘structural’ similarity between ill-defined active substances or complex mixtures of ill-defined substances of natural origin would be more difficult, due to greater variability of the substances in question.

II.2 Mechanism of action

In assessing whether two active substances act via the same mechanism, it will be assumed *a priori* that the two products have the same therapeutic indication.

The mechanism of action of an active substance is the functional description of the interaction of the substance with a pharmacological target that elicits a pharmacodynamic effect.

A pharmacological target is usually a receptor, enzyme, channel, carrier or an intracellular coupling process. Although the pharmacological target may be the same, two substances may elicit a different effect depending on the location of the target, or whether it is activated or inhibited.

The pharmacodynamic effect is the action of the active substance on the body (e.g. bradycardia). For the purpose of similarity of orphan products, the pharmacodynamic effect relevant to the “mechanism of action” is the primary pharmacodynamic effect(s) of the active substance that drives the therapeutic indication.

Differences between two active substances in terms of potency, affinity or selectivity for a common pharmacological target and/or organ or tissue distribution of the target may induce variations in its pharmacodynamic profile. However, if the differences in the above properties of the two substances do not have any influence on the primary pharmacodynamic effect which drives the therapeutic indication, then these differences are not sufficient to consider that mechanisms of action are different.

The mechanism of action is not the same when two active substances act at different pharmacological targets, even though the pharmacodynamic effect is the same. In case two active substances act at multiple targets (including subtypes of the same receptor) but share at least one common target, it should be considered whether the common target(s) explains all the pharmacodynamic properties of interest which drive(s) the therapeutic indication:

- If (a) common target(s) explain(s) all the pharmacodynamic properties of interest, both mechanisms of action are considered as the same or similar (example: atenolol and propranolol would be considered to have the same mechanism of action regarding their indication in hypertension, even if they have different selectivity and potency at • 1-receptor and • 2-receptor levels).

³ Tanimoto S, Pavlidis T (1975): A hierarchical data structure for picture processing. *Computer Graphics & Image Processing*, **4**, 104-119

⁴ Tversky A (1977): Features of Similarity. *Psychol. Rev.*, **84**, 327-352

- If (a) common target(s) does not explain all the pharmacodynamic properties of interest, the mechanisms of action are different (example: carvedilol and metoprolol share β -receptor blocking activity but their mechanisms of action differ for the treatment of severe congestive heart failure due to the additional α -receptor blocking activity of carvedilol).

When two active substances share one pharmacodynamic effect through one pharmacological target that may drive the therapeutic indication, they will be considered as having the same mechanism of action unless the applicant demonstrates that an additional pharmacological property of one of the substances has a major contribution to the overall pharmacodynamic effect that drives the therapeutic indication.

In case the mechanism(s) of action is (are) not fully known, the applicant will have to demonstrate that the two active substances act via different mechanisms.

A prodrug would be considered to have the same mechanism of action as its active metabolite.

The mode of administration and pharmacokinetic properties of a substance are not relevant to the mechanism of action.

It is, however, conceivable that the above-mentioned differences, which are not considered relevant for establishing a difference in the mechanism of action, may translate into a clinical superiority for patients. Therefore the second applicant will have to establish that the second product, although similar to the orphan medicinal product already authorised, is safer, more effective or otherwise clinically superior, to benefit from market exclusivity derogation.

II.3 Therapeutic indication

According to the EC Communication 2003/C 178/02, the same therapeutic indication means (i.e.) “the same subset of the designated condition” and two products are intended for the same indication, “for example, where there is a significant overlap of the target population”.

The comparison of the therapeutic indications will be based on the orphan condition. As the therapeutic indication does not always cover the complete orphan condition, it may be necessary to compare subsets. If one orphan medicinal product has been granted an indication in a subset of the designated condition, any application in another subset will have to establish that this new subset is clinically meaningful. If there is an overlap of the target populations, the second applicant should estimate its extent.

III **Processing of other derogations**

(See section I.2 on information to be submitted by the applicant)

As stated in paragraph 3 of Article 8 of Regulation (EC) No. 141/2000, a marketing authorisation may be granted, for the same therapeutic indication, to a similar medicinal product if:

- (a) the holder of the marketing authorisation for the original orphan medicinal product has given his consent to the second applicant, or
- (b) the holder of the marketing authorisation for the original orphan medicinal product is unable to supply sufficient quantities of the medicinal product.

For derogation (a), the Competent Authority will check at the time of the validation that the second applicant has provided the signed consent of the marketing authorisation holder for the original orphan medicinal product, in order to validate the application.

For derogation (b), at least two months before submitting the dossier, the second applicant will have to provide the Competent Authority with a report supporting their submission that the marketing authorisation holder for the original orphan medicinal product is unable to supply sufficient quantities of the medicinal product in the EU Community. This report will be circulated to Member States for comments within one month. The Competent Authority will also liaise with the MAH of the original product(s), inviting them to submit comments in writing within one month. The Competent Authority will issue a position within two months following receipt of the second applicant’s report. Criteria for sufficient or insufficient supply will be issued in separate guidance.

IV Assessment of “clinical superiority”

The CHMP will assess “clinical superiority” as defined in article 3 of Commission regulation (EC) No. 847/2000:

“(d) "clinically superior" means that a medicinal product is shown to provide a significant therapeutic or diagnostic advantage over and above that provided by an authorised orphan medicinal product in one or more of the following ways:

(1) greater efficacy than an authorised orphan medicinal product (as assessed by effect on a clinically meaningful endpoint in adequate and well controlled clinical trials). Generally, this would represent the same kind of evidence needed to support a comparative efficacy claim for two different medicinal products. Direct comparative clinical trials are generally necessary, however comparisons based on other endpoints, including surrogate endpoints may be used. In any case, the methodological approach should be justified;

or

(2) greater safety in a substantial portion of the target population(s). In some cases direct comparative clinical trials will be necessary;

or

(3) in exceptional cases, where neither greater safety nor greater efficacy has been shown, a demonstration that the medicinal product otherwise makes a major contribution to diagnosis or to patient care.”

Further guidance could be proposed in the light of future regulatory experience. The basis for “clinical superiority” according to the orphan legislation will be described in the European Public Assessment Report but no claim based on “clinical superiority” would normally be included in the summary of product characteristics.

V Glossary of the abbreviations used

BWP:	Biotechnology Working Party
CHMP:	Committee for Medicinal Products for Human Use
COMP:	Committee for Orphan Medicinal Products
EC:	European Commission
EMA:	European Medicines Agency
EU:	European Union
INN:	International Non-Proprietary Name
MAA:	Marketing Authorisation Application
MAH:	Marketing Authorisation Holder
MR:	Mutual Recognition
MRFG:	Mutual Recognition Facilitation Group
NCA:	National Competent Authority
QSE:	Quality, Safety and Efficacy
QWP:	Quality Working Party
RMS:	Reference Member State
WHO:	World Health Organisation

Appendix 1:

Examples to illustrate cases: 'structural similarity' of macromolecules

Regulation 847/2000, in article 3.3(c)2, gives definitions of similarity in the context of orphan medicinal products for macromolecules. These definitions are explicit. However, additional guidance is provided by giving some examples of what would and what would not be considered similar in terms of having the same principal molecular structural features (but not necessarily all of the same molecular structural features) and which act via the same mechanism.

The examples given below are not intended to be exhaustive.

Article 3.3(c) 2.1 *proteinaceous* substances where:

- the difference is due to infidelity of transcription or translation,
- the difference in structure between them is due to post-translational events (such as different glycosylation patterns) or different tertiary structures.
- the differences in the amino acid sequence are not major. Two pharmacologically related protein substances of the same group (for example, two biological compounds having the same International Nonproprietary Name [INN] sub-stem) would be considered similar.
- the monoclonal antibodies bind to the same target epitope. These would normally be considered similar.

In the context of the orphan regulation, interferon betas would be considered similar. Interferon alphas would be considered similar. However an interferon beta would normally be considered to be different from an interferon alfa. Factor VIIIs (Octocogs) would be considered to be similar whether plasma derived or recombinant or truncated. Octocogs (factor VIIIs) would be considered to be different from Nonacogs (factor IXs). Somatropin (human growth hormone) and methionyl human growth hormone would be considered to be similar. The INN substem for G-CSFs is '-grastim'; glycosylated and non-glycosylated granulocyte colony stimulating hormone (G-CSF) would be considered similar. Pegylated and non-pegylated versions of proteins would be considered similar. The same protein whether produced by biotechnology or by synthesis would be considered similar. Two monoclonal antibodies targeting the same antigen would normally be considered similar.

Article 3.3(c) 2.2

polysaccharide substances having identical saccharide repeating units, even if the number of units varies and even if there are post-polymerisation modifications (including conjugation).

In the context of the orphan regulation, heparins (either high or low molecular weight) would be considered to be similar. Starches would be considered similar. A conjugated version of a vaccine would be considered to be similar to the unconjugated version.

Article 3.3(c) 2.3 *polynucleotide substances* (including gene transfer and antisense substances), consisting of two or more distinct nucleotides where

- the difference in the nucleotide sequence of the purine and pyrimidine bases or their derivatives is not major. Therefore, for antisense substances, the addition or deletion of nucleotide(s) not significantly affecting the kinetics of hybridisation to the target would normally be considered to be similar. For gene transfer substances, unless the differences in the sequence were significant the substances would normally be considered similar.
- the difference in structure between them relates to modifications to the ribose or deoxyribose sugar backbone or to the replacement of the backbone by synthetic analogues.
- the difference is in the delivery system or in the vector system.

In the context of the orphan regulation, the differences in the gene sequence would need to be significant for the two genes not to be considered similar. For example, two genes coding for two pharmacologically related proteins of the same group would be considered similar; thus two genes coding for an interferon alfa would be considered similar (either coding for the same amino acid sequence by using different codons, allelic variants, or coding for an interferon alfa of different amino acid sequence). The same gene placed in a different vector or transfer system (e.g. retrovirus, adenovirus, liposomes, etc) would be considered to be similar.

Article 3.3(c) 2.4: <i>closely related complex partly definable substances</i> (such as two related viral vaccines, related cell therapy products).

Consideration of similar active substances is in the context of acting via the same mechanism and for the same indication. Currently INNs are not given to vaccines. In the context of the orphan regulation, two vaccines consisting of measles virus would be considered similar. Two Pertussis vaccines (irrespective of whether whole cell or acellular) would be considered similar. Vaccines consisting of pneumococcal polysaccharides (whether conjugated or not) would be considered similar. Measles vaccines would be considered different to pertussis vaccines.

Two cell therapy products based on Islets of Langerhans cells for the treatment of diabetes would be considered similar.

Appendix 2:

Examples to illustrate cases 'structural similarity' of chemically-synthesised active substance

This appendix also provides specific information for chemically-synthesised peptides and for radiopharmaceutical substances, in the context of the orphan regulation.

Examples are given in the form of questions and answers, beginning with given information which is defined and concrete, then proceeding to situations which are more difficult to judge.

Chemically-synthesised active substances

1. Are the active substances identical? Do they have the same INN?

Substances which are identical are regarded as 'similar' in the context of Commission Regulation (EC) n°847/2000, Art 3,3,c)

2. If the INNs are different, do the INNs contain the same substem?, e.g. "-prost"

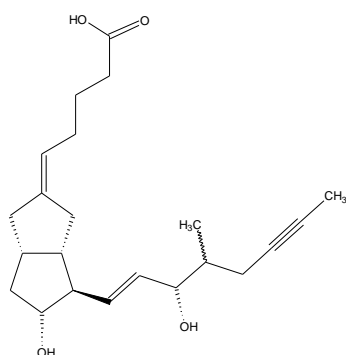
Substances containing the same INN substem would normally be regarded as similar unless there are major structural differences (see below). The following examples may illustrate this. They are not exhaustive and it is assumed that there can reasonably be a common indication or mechanism of action. They are chosen only to illustrate the chemical structural principles involved, other things being equal.

(However, note that the INN often has *functional* connotations rather than structural).

'≈' means 'could be regarded as structurally similar to'

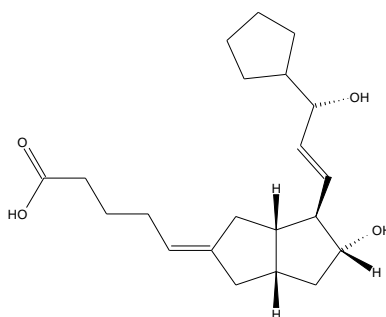
'•' means 'could not be regarded as structurally similar to'

Prostaglandins



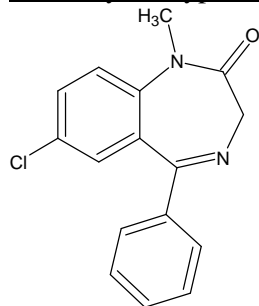
Iloprost

≈



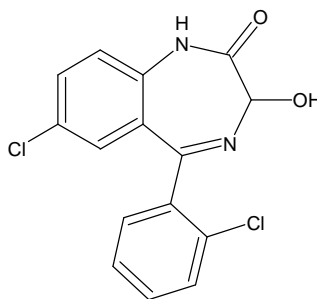
ataprost

Anxiolytics/hypnotics:



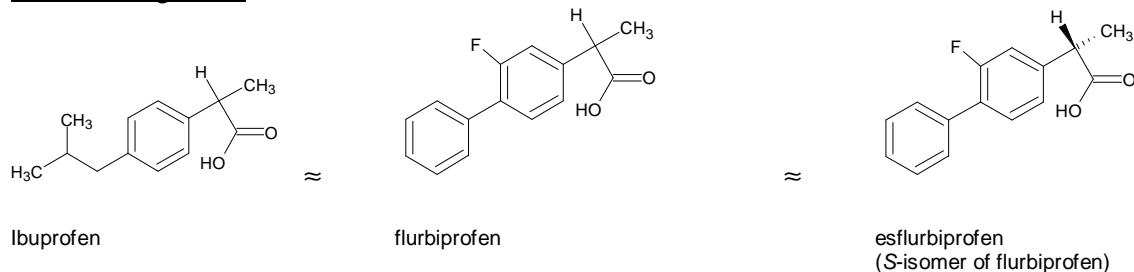
diazepam

≈

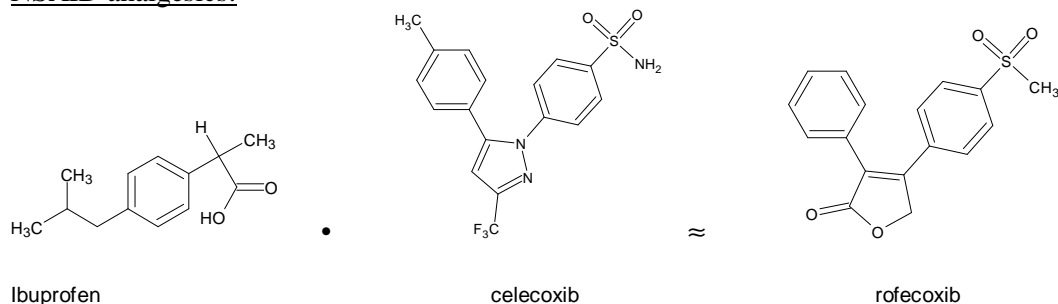


oxazepam

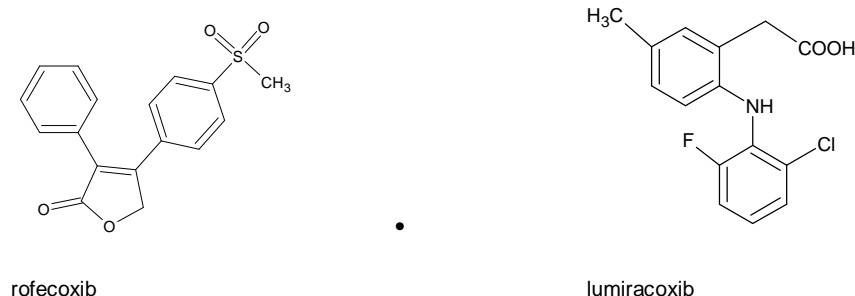
NSAID analgesics:-



NSAID analgesics:



However, despite the common INN sub-stem, major structural differences are evident in the case of rofecoxib and lumicoxib, and therefore they may not be regarded as structurally similar. i.e.:



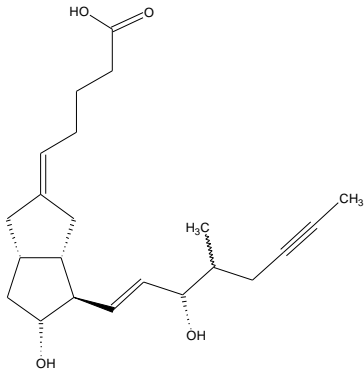
3. From a consideration of the structures, redrawn if necessary, can it be concluded that the molecules possess the same principal molecular structural features (but not necessarily all of the same molecular structural features)?

If yes, the molecules may be judged to be structurally similar, ref. Article 3(3) subparagraph c - unless otherwise justified.

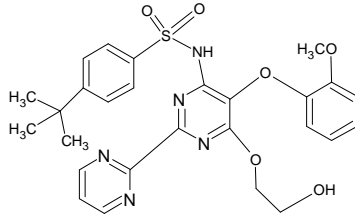
4. Can it be concluded that the differences relate only to 'minor' changes in the molecular structure, such as a structural analogue?

If yes, the molecules may be judged to be structurally similar, ref. Article 3(3) subparagraph c.1 - unless otherwise justified.

The above two questions relate to the 'overarching' definition of structural similarity - Article 3 (3,3,c) and a high level subsection – Article 3,3,c,1). Some examples may serve to illustrate the interpretation of ...*same principal molecular structural features*... and ...*minor changes in molecular structure*... as applied to chemical substances. Again, these examples are not exhaustive and it is assumed that there can reasonably be a common indication or mechanism of action. They are chosen only to illustrate the chemical structural principles involved, other things being equal:

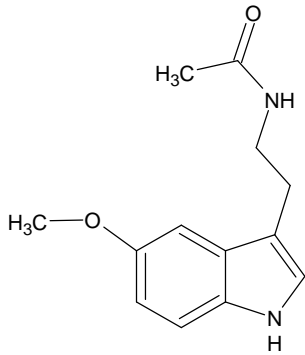


Iloprost

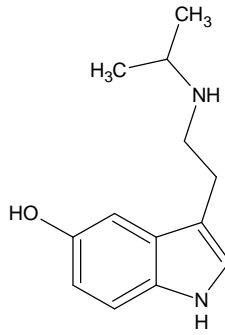


bosentan

Both have a common indication in pulmonary hypertension, but -
 No principal molecular structural features in common
 Differences in structure are not minor



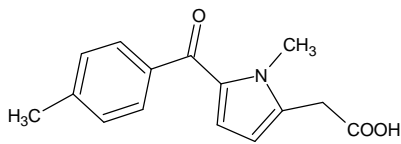
Melatonin



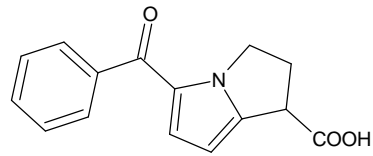
bufotenine

≈

Both are modulators of the serotonin pathway
 Structural analogues,
 Same principal molecular structural features,
 Differences in structure are minor



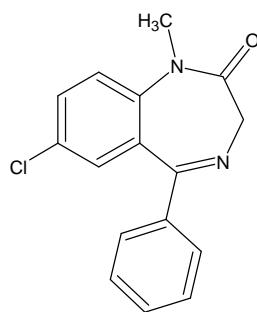
Tolmetin



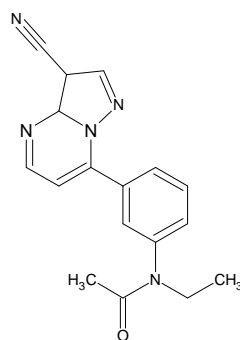
ketorolac

≈

Both are NSAIDs
 Structural analogues,
 Same principal molecular structural features,
 Differences in structure are minor



Diazepam



Zaleplon

• Both have CNS activity as anxiolytic/hypnotics
 However, No common principal structural molecular features
 Differences in structure are not minor

Arguments based on the overarching definition may come into conflict with INN substem arguments and other arguments set out in other subsections of Article 3(3) subparagraph c. Unless otherwise justified, the overarching definition would normally take precedence. e.g. the following cases can be foreseen :

Regulation (EC) No. 847/2000	Similarity condition		
Article 3(3) subparagraph c Overarching definition	Same principal molecular structural features?	No	Yes
Article 3(3) subparagraph c.1	Changes in molecular structure are only minor, not major?	No	Yes
	Same INN substem?	Yes	No

• probably not similar
 • probably similar

Eventually, such comparisons may need to be decided on a case-by-case basis taking into account all parts of the legislation which are considered to be relevant to the comparison in question.

Chemically-synthesised peptides:

1 Can the difference in amino acid sequence be considered as ‘not major’?

If yes, the molecules may be judged to be structurally similar, ref. Article 3(3) subparagraph c, subsection 2.1, 3rd indent, unless otherwise justified.

e.g. two pharmacologically-related protein substances of the same group (for example two compounds having the same INN sub-stem) would normally be regarded as similar.

In principle the considerations given in appendix 1 for proteinaceous substances may be applied to chemically-synthesised proteins. Note that identical proteins would be considered similar, regardless of whether they are produced by synthesis or by biotechnology.

2 For chemically-synthesised polynucleotide substances (including antisense substances) consisting of two or more distinct nucleotides: Can the difference in the nucleotide sequence of the purine and pyrimidine bases or their derivatives be considered as ‘not major’?

If yes, the molecules may be judged to be structurally similar, ref Article 3(3) subparagraph c, subsection 2.3, 1st indent - unless otherwise justified.

e.g. for antisense substances, the addition or deletion of nucleotide(s) not significantly affecting the kinetics of hybridisation to the target would normally be considered similar.

In principle the considerations given in appendix 1 for polynucleotide substances may be applied here.

For radiopharmaceutical substances:

Are there differences in radionuclide, ligand, site of labelling or carrier molecule-radionuclide coupling mechanism linking the molecule and radionuclide?

If yes, the molecules may be judged to be structurally similar, ref Article 3(3) subparagraph c subsection 3 - unless otherwise justified.

e.g. radiopharmaceutical substances differing in the characteristics described above could be considered similar, provided they have the same mechanism of action.