

Commission notice on the application of Articles 3, 5 and 7 of Regulation (EC) No 141/2000 on orphan medicinal products

(2016/C 424/03)

A. INTRODUCTION

Regulation (EC) No 141/2000 ⁽¹⁾ on orphan medicinal products aims to stimulate medicinal product research in the area of rare diseases. It lays down a Union procedure for the designation of orphan medicinal products and provides incentives for research and development on such products and placing them on the market.

In accordance with Articles 3(2) and 8(4) of the Regulation, the Commission adopted Commission Regulation (EC) No 847/2000 ⁽²⁾, which governs application of the criteria for designating orphan medicinal products and defines the concepts 'similar medicinal product' and 'clinical superiority'.

On 29 July 2003, the Commission issued a Communication on Regulation (EC) No 141/2000 ⁽³⁾ which considered points in relation to its Articles 3 (criteria for designation), 5 (procedure for designation and removal from the register) and 7 (Union marketing authorisation).

This notice replaces the Communication. Its scope is the same: it is intended to facilitate the application of Articles 3, 5 and 7 of Regulation (EC) No 141/2000. This notice is not legally binding and, in case of doubt, reference should be made to the relevant Union directives and regulations. When reading this text, it is important to appreciate that the legal requirements of the Union pharmaceutical legislation must be met.

The procedure relating to orphan medicinal products consists of two separate phases ⁽⁴⁾:

- i. designation – this can take place at any stage of development prior to the submission of a marketing authorisation application, provided that the sponsor can establish that the criteria in Article 3 of the Regulation are met. Designation has no effect on parallel developments by different sponsors. It is a tool to identify candidate products in a transparent way and to make them eligible for financial incentives. Designation will be confirmed by a separate Commission decision for each candidate product and the designated product will be entered in the Community Register for Orphan Medicinal Products (Article 5 of the Regulation); and
- ii. marketing authorisation.

B. CRITERIA FOR DESIGNATION (ARTICLE 3(1))

The requirements for designation as an orphan medicinal product, as laid down in Article 3(1) of the Regulation, are as follows:

- i. the product is intended for the diagnosis, prevention or treatment of a rare condition or the marketing of the product intended for the diagnosis, prevention or treatment of a life-threatening or serious condition would not generate sufficient return to cover the investment made; and
- ii. there is no satisfactory treatment for the condition in question in the EU or, if there is, the product in question will be of significant benefit to patients affected by that condition.

1. Orphan condition

A condition is understood as any deviation from the normal structure or function of the body, as manifested by a characteristic set of signs and symptoms (typically a recognised distinct disease or a syndrome).

The condition proposed by the sponsor is the starting point for the scientific evaluation. When considering an application for orphan designation, the European Medicines Agency's Committee for Orphan Medicinal Products (COMP) may consult the sponsor if it does not agree with the original proposed condition. The COMP may take into account the available data to determine the condition (e.g. it may consider that it is broader than the sponsor's proposal). In such cases, it will issue an opinion for the designation of the condition it considers suitable.

⁽¹⁾ Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products (OJ L 18, 22.1.2000, p. 1).

⁽²⁾ OJ L 103, 28.4.2000, p. 5.

⁽³⁾ Communication from the Commission on Regulation (EC) No 141/2000 of the European Parliament and of the Council on orphan medicinal products (OJ C 178, 29.7.2003, p. 2).

⁽⁴⁾ Case T-74/08, *Now Pharm AG v European Commission*, ECLI: EU:T:2010:376, paragraph 33.

2. Prevalence or potential return on investment criteria

(a) Prevalence criterion

With regard to the criteria envisaged for designation of an orphan medicinal product, the Regulation does not distinguish between medicinal products intended for the treatment of a condition and those intended for the diagnosis or prevention of a condition (e.g. vaccines).

Prevalence calculation for medicinal products intended for the diagnosis or prevention of a condition

In the case of a product intended for diagnosis or prevention, the population 'affected by' the condition may be determined in various ways.

The objective of the Regulation is to provide incentives for the development of orphan medicinal products where such incentives are needed. Therefore, in the case of medicinal products intended for prevention (e.g. vaccines), the Commission considers that the prevalence calculation of those persons affected by the condition should be based on the population to which such a product is expected to be administered on an annual basis. For example, following successful vaccination campaigns, although the vaccinated population is very large, the prevalence of the condition in question may be very low. The prevalence calculation in these cases should be based on the population vaccinated on an annual basis.

Prevalence of a condition outside the European Union

Communicable diseases (e.g. Ebola, Zika virus or avian influenza) can very rapidly become a serious threat to public health. The development of treatments for such diseases may be economically unattractive, so that serious public health threats remain unaddressed in developing countries, but also in the EU. Article 3(1)(a) of the Regulation requires that, to be considered as orphan, conditions must affect '*not more than five in 10 000 persons in the Community [European Union]*'. Since this refers only to the number of persons affected within the EU, the prevalence of the disease or condition outside the EU has no influence on the application of the criteria. A medicinal product intended to diagnose, prevent or treat a condition which affects a large number of people in certain non-EU countries, but which has a low prevalence or a prevalence of approximately zero in the EU, may be eligible for designation as an orphan medicinal product with respect to the prevalence criterion, and if all other criteria are met, eligible for the benefits set out in the Regulation. Where prevalence in the EU is currently approximately zero, account should be taken of the risk that persons in the EU may become affected.

(b) Potential return on investment criterion

Medicinal products intended for a life-threatening, seriously debilitating or serious and chronic condition are eligible for orphan designation even where prevalence is greater than five in 10 000, if the marketing of the product is unlikely to generate a sufficient return on investment.

This will be assessed on the basis of all past and future development costs and expected revenues.

3. Intention to diagnose, prevent or treat (medical plausibility)

Preclinical and/or preliminary clinical data are generally required to support the rationale for the development of the product in the proposed condition.

The EU legislation on orphan medicinal products aims to encourage the development of medicines for rare diseases that occur so infrequently that the costs of development and bringing to market would not be recovered by the expected sales of the product. In applications where the proposed orphan indication refers to a subset of a particular condition, a justification for restricting the use of the product would be needed. Patients in the subset should present distinct and unique evaluable characteristics with a plausible link to the condition and such characteristics should be essential for the product to carry out its action. In particular, the genetic subtype/profile and pathophysiological characteristics associated with the subset should be so closely linked to the diagnostic and/or preventive and/or treatment action of the product that the absence of these characteristics will render the product ineffective in the rest of the population suffering from the condition.

There is an increasing shift towards personalised medicine, leading to the stratification of the patient population. Nevertheless, 'subsetting' a condition with the use of biomarkers will not be acceptable unless the sponsor provides solid scientific evidence that the activity of the product would not be shown on the larger population.

4. Satisfactory method authorised in the Union

Article 3(1)(b) requires the sponsor to establish '*that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the Community [European Union]*'. In order to ensure consistency of application and to help sponsors provide appropriate justification, it is considered important to clarify the notion of 'satisfactory' in this context. Commission Regulation (EC) No 847/2000 requires the sponsor to provide details of '*existing methods, which may include authorised medicinal products, medical devices or other methods of diagnosis, prevention or treatment which are used in the Community [European Union]*'.

A marketing authorisation is granted if the benefit/risk assessment is positive. Therefore, at the time a marketing authorisation is granted in accordance with EU legislation, the product is considered to be a 'satisfactory method', within the meaning of Article 3(1)(b). This being the case, sponsors for orphan designation should seek to show an assumption of significant benefit as compared with existing authorised medicinal products in accordance with the second part of Article 3(1)(b), rather than seeking to show that such products are not a satisfactory method.

In this context, a medicinal product authorised in one Member State of the EU is generally deemed as being '*authorised in the Community [European Union]*'. It is not necessary for it to have Union authorisation or to be authorised in all Member States. However, medicinal products taken into consideration should be authorised for the treatment of the disease as such or, at the very least, address exactly the same set of symptoms.

Any reference to an authorised medicinal product must be limited to the terms of the marketing authorisation. Therefore, a product that is administered or applied outside the approved summary of product characteristics ('off-label' use) cannot be considered a satisfactory method for the purposes of Article 3(1)(b).

Commonly used methods of diagnosis, prevention or treatment that are not subject to marketing authorisation (e.g. surgery, radiotherapy, medical devices) may be considered satisfactory if there is scientific evidence of their efficacy and safety. Such evidence would refer to clinical guidelines from European medical societies or published scientific evidence. In certain cases, medicinal products prepared for an individual patient in a pharmacy according to a medical prescription, as referred to in Article 3(1) of Directive 2001/83/EC (commonly known as the 'magistral formula'), or according to the prescriptions of a pharmacopoeia and intended to be supplied directly to patients served by the pharmacy, as referred to in Article 3(2) of that Directive (commonly known as the 'official formula'), may be considered as satisfactory treatment if they are well known and safe and this is a general practice in the EU. If the product proposed for designation is not authorised to be placed on the market, patients in the EU may still be treated with it if it is prepared in a pharmacy. On the other hand, a product prepared in a hospital under a hospital exemption scheme (see Article 3(7) of Directive 2001/83/EC) should not be considered a satisfactory method of diagnosis, prevention or treatment of a condition.

5. Significant benefit

In accordance with Article 3(1)(b), a medicinal product may be designated as an orphan product even if a treatment exists for the condition in question, provided that it represents a 'significant benefit' to those affected by the condition. 'Significant benefit' is established by means of comparison with existing authorised medicinal products or methods, not just by assessing the intrinsic qualities of the product in question ⁽¹⁾.

'Significant benefit' is defined in Article 3(2) of Regulation (EC) No 847/2000 as '*a clinically relevant advantage or a major contribution to patient care*'.

The purpose of the legislation is to encourage and reward innovative treatments. These require investment in research and in the development of potential improved medicinal products that can bring meaningful advantages for patients ⁽²⁾. It is clear from Article 3(1)(b) of Regulation (EC) No 141/2000 and the spirit underlying the system it establishes that the criteria for a finding of significant benefit are strict ⁽³⁾. For example:

— '*a clinically relevant advantage*' may be based on:

- improved efficacy for the entire population suffering from the condition or a particular population subset or a subset that is resistant to the existing treatments; or
- a better safety profile or a better tolerability for the entire population suffering from the condition or for a particular subset.

In both cases, the claim should be based on clinical experience:

— '*a major contribution to patient care*' may be based on:

- ease of self-administration, e.g. if the new treatment allows ambulatory treatment instead of treatment in a hospital only or if it has a significant impact on convenience of use and reduces treatment burden; or
- significantly improved adherence to treatment due to a change in pharmaceutical form (e.g. modified release formulation), provided there are documented difficulties with the existing form and data showing better clinical outcomes with the new form. Difficulties should be documented in peer-reviewed publications, patients' registries or therapeutic guidelines. A better clinical outcome could include better quality of life.

⁽¹⁾ Case T-74/08, *Now Pharm AG v European Commission*, ECLI: EU: T:2010:376, paragraph 46.

⁽²⁾ Case T-264/07, *CSL Behring v Commission and EMA*, ECLI: EU: T:2010:371, paragraph 94.

⁽³⁾ Case T-140/12, *Teva Pharma BV v EMA and Commission*, ECLI: EU: T:2015:41, paragraph 65.

To be regarded as making a major contribution to patient care, the product should at least be equivalent in terms of efficacy, safety and benefit/risk balance as compared with the authorised medicinal products.

'Significant benefit' should not be based on:

- possible increased supply/availability due to shortages of existing authorised products or to existing products being authorised in only one or a limited number of Member States. (Exceptions may be made if the sponsor has evidence of patient harm);
- enhancement of the pharmaceutical quality of a product in compliance with relevant Committee for Medicinal Products for Human Use (CHMP) guidelines – this is an obligation for all marketing authorisation holders; or
- a new pharmaceutical form, a new strength or a new route of administration, unless it brings a major contribution to patient care; or
- an alternative mechanism of action *per se*. However, in exceptional cases consideration may be given to those developments at the time the designation is granted. At the time the criteria are reviewed for the purposes of granting the marketing authorisation, this must translate into a clinically relevant advantage or a major contribution to patient care.

The sponsor should establish significant benefit as compared with existing authorised medicinal products and satisfactory methods at the time of designation. As there may be little clinical experience with the orphan medicinal product in question (e.g. to demonstrate better safety), the sponsor is likely to base the justification for significant benefit on assumptions of benefit at the time of designation. In all cases, the COMP should assess whether these assumptions are supported by available data supplied by the sponsor.

Protocol assistance (Article 6) is recommended to ensure appropriate clinical development of the orphan medicinal product. This can include guidance on demonstrating significant benefit as compared with authorised medicines.

6. Maintenance of orphan designation at the time of marketing authorisation

The criteria in Article 3(1) must continue to be met when the product is granted marketing authorisation as an orphan medicinal product, since (pursuant to Article 5(12)(b)) a medicinal product which, before marketing authorisation is granted, fails to meet those criteria must be removed from the register⁽¹⁾.

At this stage, companies will normally be required to provide more data than at the time of designation. For example, a claim of a better safety profile is expected to be better substantiated by data at the time of the application for a marketing authorisation. The COMP's assessment with a view to maintaining the orphan designation will be based on such data.

The significant benefit should include a quantitative element that allows the COMP to measure magnitude of effect as compared with an already authorised product. Any advantage of the designated orphan product will be considered in the context of experience with authorised products in the orphan condition, even if comparative clinical studies are not possible. In exceptional cases, if it is not possible to generate a sample big enough to provide sufficient comparative evidence, alternative methods (e.g. indirect comparisons with external data) may be used.

Granting an orphan marketing authorisation for a new pharmaceutical form of an existing medicinal product could prevent the entry of generics of the existing product on the grounds that they would be considered similar to the orphan product. Consequently, the major contribution to patient care of the new pharmaceutical form should be justified in all cases with relevant data showing meaningful benefits for patients (see above).

To meet unmet medical need and ensure early patient access, it may be appropriate to grant marketing authorisations for orphan medicinal products on the basis of a less complete package of data. In such cases, sponsors may seek a conditional marketing authorisation. Nevertheless, the limited package of data may not be sufficient to confirm significant benefit and the orphan designation may not be confirmed at the time the marketing authorisation is granted. Before considering a conditional marketing authorisation for an orphan medicinal product, it is therefore recommended to seek protocol assistance.

⁽¹⁾ Case T-140/12, *Teva Pharma BV v EMA and Commission*, ECLI:EU:T:2015:41, paragraph 66.

C. PROCEDURE FOR DESIGNATION AND REMOVAL FROM THE REGISTER (ARTICLE 5)

Article 5 lays down the procedure for designation and removal from the Community Register of Orphan Medicinal Products. Under Article 5(12)(b), a designated orphan medicinal product is to be removed from the register 'if it is established before the market authorisation is granted that the criteria laid down in Article 3 are no longer met in respect of the medicinal product concerned'.

This implies that removal on this basis must be preceded by re-evaluation by the COMP of the criteria in Article 3. Re-evaluation may lead to removal if there is evidence that the basis on which the original designation was granted has changed, for example if:

- the assumption of clinical relevant advantage or major contribution to patient care is not supported by data at the time the marketing authorisation is granted; or
- new literature data indicate that prevalence has increased between the time of the designation and the time of the marketing authorisation.

1. Justification of continued fulfilment of the criteria by the sponsor

When a sponsor submits an application for marketing authorisation for a designated orphan medicinal product, the sponsor must include the information that the product concerned has been designated. In addition, the sponsor is required to submit a report on the criteria that led to designation and up-to-date information on the continued fulfilment of those criteria.

The information will be assessed in parallel with the marketing authorisation assessment. In cases of reasonable doubt as to whether the designation criteria continue to be met, the sponsor may be invited to provide additional justification either orally or in writing.

2. Removal from the register

The responsibility for assessing the criteria for orphan designation rests solely with the Committee for Orphan Medicinal Products. The COMP is responsible for giving a scientific opinion on initial designation. As initial designation leads to the inclusion of a medicinal product in the Community Register of Orphan Medicinal Products, it follows that removal from the register pursuant to Article 5(12)(b) should take place under the same procedure, with a scientific opinion followed by a Commission decision. That decision will be part of the decision granting or amending the marketing authorisation⁽¹⁾.

3. Re-evaluation of orphan designation criteria at time of marketing authorisation — preauthorisation phase

In principle, the most appropriate time to reconsider the designation is assumed to be when marketing authorisation is about to be granted, in parallel with the expected positive opinion from the CHMP.

Where two applications for marketing authorisation for the same condition have been received by the European Medicines Agency at the same time, they might not remain in parallel. In such cases, it may be difficult for the second product to show significant benefit as compared with the first product due to the limited information available.

Where the two applications are assessed by the CHMP at the same time, the sponsor of the second product should not be required to show significant benefit as compared with the first product.

On the other hand, the second sponsor should show data supporting significant benefit as compared with the first product if the notification of marketing authorisation for it has been published in the *Official Journal of the European Union* at the time of the re-evaluation of the designation criteria by the COMP. The significant benefit may be based on indirect comparison.

4. Effect on marketing authorisation procedure of removal from the Community register

If a designated medicinal product is removed from the register after the sponsor has submitted a marketing authorisation application to the Agency, it may still be granted a Union marketing authorisation. However, the product will not be entitled to any further benefits under the Orphan Regulation (e.g. market exclusivity and future fee reductions). On the other hand, none of the benefits enjoyed prior to the removal from the register, such as fee reductions, can be recovered.

5. Time of designation and transfer to another sponsor

Article 5(1) provides that: 'in order to obtain the designation of a medicinal product as an orphan medicinal product, the sponsor shall submit an application to the Agency at any stage of the development of the medicinal product before the application for marketing authorisation is made'.

⁽¹⁾ See T-140/12, *Teva Pharma BV v EMA and Commission*, ECLI:EU:T:2015:41, paragraph 53.

Article 5(11) stipulates that an orphan designation can be transferred to another sponsor.

Reading Article 5(1) and (11) in conjunction, a sponsor can receive only one orphan designation per condition for any given medicinal product. However, a single medicinal product can be investigated in several orphan and non-orphan conditions. New subsequent formulations and routes of administration of an orphan medicinal product that has already been authorised fall within the scope of the existing orphan designation. Moreover, it is not possible to transfer an orphan designation to a sponsor who already has a marketing authorisation for the same medicinal product and condition. Any additional pharmaceutical form should be granted by varying the existing marketing authorisation. Where a sponsor applies for a separate marketing authorisation to establish a distinction between two pharmaceutical forms and avoid medication errors, the separate authorisation will be subject to the same market exclusivity period.

D. SCOPE OF UNION MARKETING AUTHORISATION (ARTICLE 7(3))

1. Designated condition versus authorised indication

Article 7(3) states that: *'the marketing authorisation granted for an orphan medicinal product shall cover only those therapeutic indications which fulfil the criteria set out in Article 3'*.

A distinction should be drawn between the procedure for designating, and that for granting marketing authorisation for, an orphan medicinal product. They are subject to different criteria, so different decisions may be taken as regards, for example, the designated condition and the authorised therapeutic indication. When evaluating an application for designation, the COMP should consider an orphan condition in broad terms in order to avoid designations relating to artificial subsets of a particular condition.

The question has been raised as to whether it is possible to authorise, in the framework of the marketing authorisation procedure, a therapeutic indication that differs from the condition that has been accepted in the designation procedure. If an orphan designation and its continuing benefits are to be maintained, it is considered necessary that the therapeutic indication applied for and that finally authorised both fall under the scope of the designated orphan condition. In order to ensure this, the sponsor may request that the designation decision be amended. Amendment is possible if the new condition differs slightly from that designated previously. If the amended designation is not accepted by the COMP or if the sponsor does not apply to amend the designation, the authorised indication will not be a designated 'orphan indication'.

Where the therapeutic indication approved through the marketing authorisation procedure is a subset of the designated orphan condition, the marketing authorisation holder will benefit from market exclusivity for the product in question, for that indication. If the same sponsor subsequently applies for marketing authorisation for a second subset of the condition, the product will not benefit from any additional period of market exclusivity, for that second authorised indication, i.e. the second indication will be covered by the market exclusivity granted on initial authorisation. This is without prejudice to the rights of a different sponsor seeking marketing authorisation for the second subset of the designated orphan condition.

Under Article 7(3), the marketing authorisation granted for an orphan medicinal product should cover only indications that fulfil the orphan designation criteria. This general principle applies to the initial marketing authorisation, but also to subsequent variations to the terms of the orphan marketing authorisation. In order to ensure compliance, the sponsor should be asked to substantiate the fulfilment of the designation criteria, if the specific scope of the variation raises justified and serious doubts in this respect.

It may be that 'significant benefit' is not established in a broad sense, covering all potential uses within an orphan condition, but only as regards certain subsets of patients or indications. Hence, the significant benefit at the initial marketing authorisation stage may be limited to second-line treatment. In such circumstances, the initial marketing authorisation for the orphan medicinal product may be limited to such a therapeutic indication as second-line treatment. However, once it has been approved, the marketing authorisation holder may wish to extend the use of the product to further therapeutic indications within the same orphan condition or to vary the indication as a first-line treatment on the basis of new evidence. While such extensions of the therapeutic indication are encouraged for the benefit of patients, the competent authorities may need to ascertain the significant benefit of this major change as compared with existing treatments in order to ensure that the variation of the terms of the orphan marketing authorisation complies with Article 7(3). This verification should cover regulatory procedures relating to the addition of a new therapeutic indication or to the modification of an existing one (e.g. major type-II variations or extension of the marketing authorisation).

2. Separate marketing authorisation

Article 7(3) allows for a sponsor of an orphan medicinal product to *'apply for a separate marketing authorisation for other indications outside the scope of this Regulation'*. On the other hand, it is also possible for the holder of marketing authorisation for a non-orphan medicinal product to develop the product in a designated orphan condition and obtain orphan designation for this new indication. In both cases, Article 7(3) requires that marketing authorisations for orphan medicinal products be handled separately from those for non-orphan medicinal products, in order to provide legal certainty that the benefits of market exclusivity under the Regulation can be ensured.
