COMMISSION NOTICE ON THE APPLICATION OF ARTICLES 3, 5 AND 7 OF REGULATION (EC) NO 141/2000 ON ORPHAN MEDICINAL PRODUCTS

CONSULTATION DOCUMENT

The purpose of this consultation is to collect views, relevant evidence and information from stakeholders to provide the European Commission with material for further developing the EU legislation on orphan medicinal products

This document does not necessarily reflect the views of the European Commission and should not be interpreted as a commitment by the Commission to any official initiative in this area.

INTRODUCTION

In 1999, the Council and the European Parliament adopted Regulation (EC) No 141/2000[1] on orphan medicinal products ("the Orphan Regulation") which introduced incentives for the research, development and marketing of medicinal products for rare diseases.

In 2003, the European Commission adopted the Communication on Regulation (EC) No 141/2000[2] in response to a number of requests for interpretation and clarification to set out its position on certain matters relating to the implementation
of the designation and market exclusivity provisions of this regulation.

The European Commission is currently in the process of considering a review of the Communication 2003/C 178/02 in order to streamline the available guidance and to adapt this Communication to the technical progress. Under the new working arrangements of the Commission such document would be presented as a Commission Notice.

This consultation is focused on a number of proposals presented below which reflect the comments and statements made by the Member States and experts at the European Medicines Agency with a view to provide the European Commission with necessary material as a basis for the new notice and, if necessary, for the revision of the Commission Regulation (EC) No 847/2000of 27 April 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 product’ and‘clinical superiority’

CONSULTATION TOPICS

Stakeholders are invited to comment on the following items which are included in the draft Notice.

Consultation item n°1: Clarification of the definition of "significant benefit"

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

[2] 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), OJ C 178, 29.7.2003, p. 2.

The Orphan Regulation aims at facilitating the placing of innovative products with a significant benefit over existing products on the European Union market. Experience over the past 15 years has shown that the 'significant benefit' is one of the key criteria for the application of the Regulation. In light of the experience, it appears useful to clarify how the sponsors need to demonstrate a significant benefit over authorised medicines. It is also important to justify in which cases a new pharmaceutical form represents a significant benefit. Furthermore, in view of the development and further integration of the European pharmaceutical market, it seems appropriate to remove the possibility of claiming a significant benefit based on a potential increased supply. Moreover, a medicinal product should have a significant benefit over authorised products or other methods of treatment used in the EU. Some Member States suggest that the medicinal products prepared in a (hospital) pharmacy should be considered in the assessment of the significant benefit.

Consultation item n°2: Encouraging the development of orphan medicinal products for communicable diseases (e.g. Ebola)

According to the orphan Regulation, a medicinal product shall be designated as orphan if the sponsor establishes that the product is intended for the treatment of a "*condition affecting not more than 5 in 10000 persons in the EU when the application is made"*. In the past, there has been discussion whether this should be understood as meaning that the prevalence in the EU should be above zero. The European Commission for example refused orphan designation for products that were intended for diseases that have been declared eradicated by the WHO. The outbreak of Ebola has shown that an infectious disease with a very low prevalence in the EU can very rapidly become a serious threat to public health. It may therefore be appropriate to apply a risk-based approach under which the prevalence equal to zero complies with the threshold of not more than 5 in 10000 people.

Consultation item n°3: Simplifying the procedure for the reassessment of orphan criteria when two authorisation application procedures are pending in parallel for two orphan medicinal products

The orphan criteria are assessed first at the time of designation and secondly at the time of the marketing authorisation. Any change in the treatment landscape, including products recently authorised, may affect the evaluation of the 'significant benefit' criterion. When the scientific assessment of two orphan medicinal products is being carried out in parallel, the applicants are unable to demonstrate the significant benefit over another medicinal product assessed positively by the European Medicines Agency only one or two months before. The European Commission therefore proposes to provide some flexibility in the assessment of orphan medicinal products in this case.

Consultation item n°4: Introducing the reassessment of the orphan criteria for a new subset of the condition when a sponsor extends the use of its product after marketing authorisation

Based on the experience with the Orphan Regulation, there are indications which show the need to clarify the necessity for a reassessment of the orphan criteria in cases where, based on new evidence, the marketing authorisation holder extends the use of its product to other therapeutic indications within the same orphan condition. Although such extensions of the initial marketing authorisation are encouraged for the benefit of patients, it may be considered that the variation of the marketing authorisation should

only be allowed after formal verification that the new therapeutic indications are of significant benefit when compared to existing treatments.
This proof of significant benefit would be required for any other new orphan marketing authorisation holder seeking authorisation for a different therapeutic indication within the same orphan condition.

Consultation item n°5: Clarifications on processing the transfer of orphan designations between sponsors

It is not possible to obtain an orphan designation for a new pharmaceutical form if the sponsor already has an orphan marketing authorisation for the same active substance, for the same condition. These applications are generally refused as the orphan designation should be requested before the marketing authorisation is granted (Article 5(1) of the Orphan Regulation). As a consequence, some companies have asked a third party to apply for the desired orphan designation, which is subsequently transferred to the original applicant. This practice can be considered as an attempt to circumvent the intention and the purpose of this provision. In addition, experience shows that this process has also delayed the placing on the market of generic medicinal products. To provide fair conditions of competition among all the companies concerned, it may be envisaged to lay down control mechanisms for the transfer of orphan designations between companies in that respect.

DRAFT NOTICE FROM THE COMMISSION ON THE APPLICATION OF ARTICLES 3, 5 AND 7 OF REGULATION (EC) N° 141/2000 ON ORPHAN MEDICINAL PRODUCTS

Regulation (EC) No 141/2000[3] of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products aims at stimulating medicinal product research in the area of rare diseases. It lays down a Union procedure for the designation of medicinal products as orphan medicinal products and provides incentives for the research, development and placing on the market of designated orphan medicinal products.

In accordance with article 3(2) and Article 8(4) of the Regulation, the Commission adopted Commission Regulation (EC) No 847/2000[4], of 27 April 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 product' and 'clinical superiority'.

On 29.7.2003, the Commission issued the Communication on Regulation (EC) No 141/2000 (2003/C 178/02).[5] This Communication considers points in relation to Articles 3 (criteria for designation), 5 (procedure for designation and removal from the register), and 7 (Union marketing authorisation) of the Regulation. In addition this Communication contains in its section D guidelines on the application of Article 8 (market exclusivity) of the Regulation, in accordance with Article 8(5) of the Regulation.

This Notice, aims at replacing Communication (2003/C 178/02). It is intended to provide guidance to sponsors submitting an application for an orphan designation and to the European Medicines Agency.

Following the scope of the Communication, the Notice focusses on points in relation to Articles 3 (criteria for designation), 5 (procedure for designation and removal from the register), and 7 (Union marketing authorisation) of the Regulation.

In view of the Communications from the Commission of 17.09.2008[6] and 19.9.2008[7] providing guidance on aspects of the application of Article 8(1), 8(2) and (3) of Regulation (EC) No 141/2000, the Notice however does not provide interpretation of Article 8 of the Regulation (market exclusivity).

The notice provides a non-legally binding tool of interpretation for the application of articles 3, 5 and 7 of Regulation (EC) N° 141/2000 on orphan medicinal products.

[3] OJ L 18, 22.1.2000, p.1.
[4] OJ L 103, 28.4.2000, p.5.
[5] 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), OJ C 178, 29.7.2003, p. 2.
[6] COMMUNICATION FROM THE COMMISSION - Guideline on aspects of the application of Article 8(2) of Regulation (EC) No 141/2000: Review of the period of market exclusivity of orphan medicinal products, 17.9.2008C(2008) 4051 final.
[7] COMMUNICATION FROM THE COMMISSION - Guideline on aspects of the application of Article 8(1) and (3) of Regulation (EC) No 141/2000: Assessing similarity of medicinal products versus authorised orphan medicinal products benefiting from market exclusivity and applying derogations from that market exclusivity, 19.9.2008, C(2008) 4077 final.

A. GENERAL

The procedure relating to orphan medicinal products is divided into two separate phases.[8] The first phase covers the designation of the product as an orphan medicinal product. Designation can take place at any stage of the development prior to the submission of a marketing authorisation provided that the sponsor can establish that the criteria are met (Article 3 of Regulation 141/2000). Designation as an orphan medicinal product 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 for each candidate product will be confirmed by a separate Commission decision and the designated candidate product will be entered in the Community Register for Orphan Medicinal Products (Article 5 of Regulation 141/2000).

The second phase covers the marketing authorisation for the product that has been designated as an orphan medicinal product.

B. CRITERIA FOR DESIGNATION – ARTICLE 3(1)

The requirements to be met in order for a medicinal product to be designated as an orphan medicinal product are laid down in Article 3(1) of Regulation (EC) No 141/2000, namely, first, that the medicinal product is intended for the diagnosis, prevention or treatment of a rare condition or that the marketing of the product would not generate sufficient return to cover the investment made and, second, that there exists no satisfactory treatment for the condition in question in the EU or, if such treatment exists, that the medicinal product in question will be of significant benefit to patients affected by that condition.

1. The orphan condition

A condition is understood as ‘any deviation(s) 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 Committee on Orphan Medicinal Products (COMP) may take into account the available data to adapt the condition under application (for example, because the Committee considers that the designable condition is broader than the one under application). In such cases, the Committee on Orphan Medicinal Products shall issue an opinion for the designation of the condition it considers suitable.

2. Prevalence or no return on investment criteria

(a) Prevalence criterion

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

[8] Cf. Case T-74/08, paragraph 33.

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

In the case of a medicinal product intended for the diagnosis or prevention of a condition, the population "affected by" the condition may be interpreted in several ways.

If a product for the diagnosis or prevention of a condition is effective, this may result in a decrease in the population actually suffering from the disease or condition to less than five in 10 thousand persons in the European Union. 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 diagnosis or prevention (e.g. vaccines), the Commission considers that the prevalence calculation of those persons affected by the condition shall 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 shall be based on the population vaccinated on an annual basis.

Prevalence of a condition outside the European Union

Communicable diseases (e.g. Ebola, avian influenza…) can become very rapidly a serious threat for public health. The development of treatments for these diseases may be economically not attractive and may lead to serious public health threat for the third countries but also for the European Union. Article 3(1)a of the Regulation requires conditions which may be considered as orphan to affect *"not more than five in 10 thousand persons in the Community [European Union]"*. Since prevalence as described in the Regulation 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 interpretation of these criteria. A medicinal product intended to treat a condition which affects a large number of people in certain third countries but which has a low prevalence or a prevalence equal to zero in the EU, may therefore 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. In cases where the prevalence is currently equal to zero in the EU, account should be taken of the risk that persons in the EU may be affected.

(b) Potential return for investment criterion

Medicinal products intended for a life-threatening, seriously debilitating or serious and chronic condition are eligible for orphan designation even when the prevalence is higher than five per 10 thousands, supposed that the marketing of the product in question is unlikely to generate sufficient return for investment.

An assessment will be based on all costs (past and future development costs) and expected revenues.

3. Intention to diagnose, prevent or treat (Medical Plausibility)

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

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 developing and

bringing to the market would not be recovered by the expected sales of the medicinal product. In applications where the proposed orphan indication refers to a subset of a particular condition, a justification for restricting the use of the medicinal product would be needed. Patients in the subset should present distinct and unique evaluable characteristic(s) with a plausible link to the condition and such characteristics would have to be essential for the medicinal product to carry out its action. In particular, the genetic subtype/profile, pathophysiological characteristics associated with this subset should be closely linked to the diagnostic, and/or preventive, and/or treatment action of the medicinal product in such a way 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's population. Nevertheless, sub-setting a condition with the use of biomarkers will not be acceptable unless the sponsor provides solid evidence that the activity of the product should not be shown on the larger population.

4. Satisfactory method authorised in the Union

Article 3(1)(b) states that the sponsor has 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 aid applicants in providing appropriate justification, it is considered important to clarify the notion of "satisfactory" method. In this context, Commission Regulation (EC) 847/2000 asks the applicant to provide details of the "*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 risk/benefit assessment is positive. Therefore, at the time of the grant of a marketing authorisation in accordance with EU legislation, the authorised medicinal product is considered to be a satisfactory method as referred to in Article 3(1)b. This being the case, applicants for orphan designation should seek to show an assumption of significant benefit over any existing authorised medicinal product in accordance with the second part of paragraph Article 3(1)(b), rather than seeking to show that an existing authorised medicinal product is not a satisfactory method.

In this context, a medicinal product authorised in one Member State of the EU is generally deemed to fulfil the criteria of "*authorised in the Community [European Union]"*. It is not necessary for the product to have either a Union authorisation or for it 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 for its symptoms.

Any reference to an already authorised medicinal product can only refer to the terms of the marketing authorisation. Therefore a medicinal product which is administered or applied not in accordance with the approved Summary of Product Characteristics of the product ["off-label" use] cannot be considered as 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, medicinal products prepared in a (hospital) pharmacy) may be considered satisfactory methods if there is scientific evidence as to the value of such method(s). The scientific evidence would refer

to scientific and medical literature or any other relevant information e.g. clinical guidelines by European medical societies.

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 that condition. Establishing significant benefit takes place in the context of a comparison with existing authorised medicinal products or methods and cannot be limited to an assessment of the intrinsic qualities of the product in question without comparing them with the intrinsic qualities of the authorised methods.[9]

Significant benefit is defined in Article 3(2) of Commission Regulation (EC) 847/2000 as "*a clinically relevant advantage or a major contribution to patient care.*"

It is apparent from Article 3(1)(b) of Regulation No 141/2000 and the spirit underlying the system established by that regulation that the criteria for a finding of a significant benefit are strict.[10] The purpose of the legislation is to encourage and reward innovative treatments. It implies an investment in research and development of the potential improved medicinal product that can bring meaningful advantages for the patients.[11]

For example, "*a clinically relevant advantage*" may be considered based on :

- An improved efficacy for the entire population suffering from the condition, for a particular population sub-set or for a sub-set of the population which is resistant to the existing treatments. The claim should be based on clinical experience;

- A better safety profile or a better tolerability for the entire population suffering from the condition or a particular population sub-set. The claim should be based on clinical experience;

For example, "*a major contribution to patient care*" may be considered based on:

– Ease of self-administration e.g. if the new treatment allows ambulatory treatment instead of treatment in a hospital only;

– Important improvement in adherence to treatment by changing the pharmaceutical form (e.g. Modified released formulation) only if there are documented difficulties with the existing form and if there are data showing better clinical outcome with the new form;

Significant benefit should not be considered based on:

- A possible increased supply/availability due to shortages of existing authorised products or due to existing products authorised only in one or a limited number of Member States. Exceptions may occur if the sponsor has evidence of patient harm;

- Enhancement of the pharmaceutical quality of a product in compliance with the relevant Committee on Medicinal Products for Human Use (CHMP) guidelines which is a part of the obligation of every marketing authorisation holder;

[9] Case T-74/08, paragraph 46.
[10] Case T-140/12, paragraph 65.
[11] Case T-264/07, paragraph 94.

- An alternative mechanism of action per se, to be sufficient for the assumption of significant benefit. It needs to be translated into a clinically relevant advantage or a major contribution to patient care.

The applicant is required to establish significant benefit compared with existing authorised medicinal products or 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 justification for significant benefit is likely to be made on assumptions of benefit by the applicant, at the time of designation. In all cases the Committee on Orphan Medicinal Products is required to assess whether or not these assumptions are supported by available data supplied by the applicant.

Protocol Assistance is recommended to ensure an appropriate clinical development of the orphan medicinal product. Protocol assistance can also include guidance to demonstrate significant benefit over authorised medicines.

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

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

At this stage of the development, companies will be required to provide more data than at the time of designation. For example, the improved safety claim is expected to be better substantiated by data at the time of the application for a marketing authorisation. The assessment by the Committee on Orphan Medicinal Products regarding the maintenance of the orphan designation will be based on these data.

The significant benefit should consider a quantitative element that allows the Committee on Orphan Medicinal Products to measure the magnitude of the effect based on direct or ,when not possible, indirect comparative clinical trials with already authorised medicinal products. Any advantage of the designated orphan medicinal product will be considered in the context of experience with authorised products in the orphan condition even if comparative clinical studies are not always possible. In exceptional cases, if it is not possible to generate a sample size big enough to provide statistically comparative evidence or due to the heterogeneous patients population, it would be possible to adapt clinical trials designs and alternative methods (such as indirect comparative data, historical data).

Where protocol assistance for the justification of significant benefit has been received in accordance with Article 6 of the Regulation, the review will also comprise the assessment on how the sponsor has taken into account the advice given.

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

[12] T-140/12, para. 66.

To meet unmet medical need and ensure early patient access, it may be appropriate to grant marketing authorisations to orphan medicinal products on the basis of less complete package of data. In such cases, applicants may seek a conditional marketing authorisation. Nevertheless, the limited package of data may not be sufficient to confirm the significant benefit and the orphan designation may not be confirmed at the time of marketing authorisation. Before considering a conditional marketing authorisation for an orphan medicinal product it is therefore highly recommended to seek protocol assistance. The European Medicines Agency is fostering collaboration between the scientific committees to ensure consistency between the confirmation of the 'unmet medical need' for the conditional marketing authorisation and the 'significant benefit' of the purpose of the orphan designation.

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

Article 5 lays down the procedure for designation and removal from the register.

In accordance with Article 5(12)(b) of the Regulation, a designated orphan medicinal product is to be removed from the Community Register of Orphan Medicinal Products "*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 a removal on this basis must be preceded by a reevaluation by the Committee on Orphan Medicinal Products of the criteria laid down in Article 3. Removal in these circumstances might occur 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 of marketing authorisation;

- the prevalence has increased between the time of the designation and the time of the marketing authorisation following new literature data.

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

When a sponsor submits an application for marketing authorisation for a designated orphan medicinal product, he/she shall include the information that the product concerned has been designated as an orphan medicinal product. In addition the sponsor is requested to submit a report on the criteria that led to the designation of the product as an orphan medicinal product and updated information on the current fulfilment of these criteria.

The information will be assessed in parallel to the marketing authorisation assessment.

In case of reasonable doubt as to whether the criteria for designation 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 on Orphan Medicinal Products. The Committee on Orphan Medicinal Products 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) must follow the same procedure of scientific opinion followed by a decision of the Commission in accordance with Article 5(8).

For the orphan medicinal products approved under the conditional marketing authorisation, further data will be generated post authorisation as part of the specific obligations and are reviewed on an annual basis in the context of the review of the benefit risk balance by the European Medicines Agency. In the light of the updated data at the end of the fifth year as provided in Article 8.2 of Regulation 141/2000, a Member State may inform the Agency that the criterion on the basis of which market exclusivity was granted may not be met and the agency shall then initiate the procedure laid down in Article 5 of Regulation (EC) No 141/2000.

3. Reevaluation of orphan designation criteria at time of marketing authorisation – preauthorisation phase

The most appropriate time to reconsider designation is principally assumed when the marketing authorisation of a designated orphan medicinal product is imminent, that is at around the time of an expected positive opinion from the Committee for Medicinal Product for Human use (CHMP).

When two procedures for granting marketing authorisations for the same condition are pending in parallel before the European Medicines Agency, they might not be concluded at the same time. In such situation, it may be difficult for the second product to show significant benefit over the first authorised product. If the two applications are validated and assessed by the CHMP at the same time, the sponsor for the second product should not be required to show significant benefit over the first product.

On the other hand, when the procedures for the simultaneous marketing authorisation applications do not remain in parallel and the positive opinion for the second product compared to the first product is delivered by the CHMP with a difference in time of two CHMP meetings or more, the second sponsor should show data supporting the significant benefit over the first product. Moreover, the significant benefit may be based on indirect comparison.

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

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, it is understood that the medicinal product cannot be entitled to any further benefits provided for by 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 the designation and transfer to another sponsor

Article 5 (1) of the Regulation lays down 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 in the development of the medicinal product before the application for marketing authorisation is made."*

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

A combined reading of these provisions implies that a sponsor can only receive one orphan designation per medicinal product and per condition. New subsequent formulations, route of administrations of the orphan medicinal product already authorised fall within the scope of the existing orphan designation. Moreover, it is not possible to transfer an orphan designation to an applicant who has already a marketing authorisation for the same medicinal product and condition. Any additional pharmaceutical forms should be granted by varying the existing marketing authorisation. In case an applicant submits a separate marketing authorisation for providing a distinction between two pharmaceutical forms and avoid medication errors, this separate marketing authorisation will be subject to the same market exclusivity period.

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

1. Designated condition vs. authorised indication

Article 7.3 of the Regulation 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"*.

The procedures for designating a medicinal product as an orphan medicinal product and for granting a marketing authorisation of an orphan medicinal product have to be distinguished. They are subject to different criteria. Therefore, different decisions may be taken relating to, for example, the designated condition and the authorised therapeutic indication. When evaluating an application for designation, the Committee on Orphan Medicinal Products will consider an orphan condition in broad terms in order to avoid designations related to artificial subsets of a particular condition.

There have been questions regarding the possibility of having a therapeutic indication authorised in the framework of the marketing authorisation procedure, which is different from the condition that has been accepted in the designation procedure. If an orphan designation and its continuing benefits are to be maintained both the therapeutic indication applied for and the therapeutic indication finally authorised are considered necessary to fall under the scope of the designated orphan condition. In order to ensure this the sponsor may request to amend the designation decision, prior to the submission of the MA application or during the process of assessment. The amendment is possible when the therapeutic indication is only slightly different from the condition previously designated. If the amended designation is not accepted by Committee on Orphan Medicinal Products or if the applicant does not apply to amend the designation, the authorised indication will not be a designated 'orphan indication'.

In some cases the initial marketing authorisation for an orphan medicinal product may cover with its authorised indications only a subset of the designated orphan condition. If the same sponsor varies subsequently the marketing authorisation to extend the use of its product for a second subset of the designated orphan condition, the product will not benefit from any additional period of market exclusivity, for that second authorised indication, ie the second authorised indication will be covered by the market exclusivity granted on initial authorisation.

It is not uncommon that 'significant benefit' is not established in a broad sense covering all potential uses within an orphan condition, but instead limited to certain subsets in terms of patients or indications. For example, it may be the case that the significant benefit at the initial marketing authorisation stage is limited to second line treatment. In those circumstances the initial marketing authorisation for the orphan medicinal product will be limited to such a therapeutic indication as second line treatment. However, once 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 based on new evidence. While such extensions of the initial marketing authorisation are encouraged for the benefit of patients, the significant benefit of this extension compared to existing treatments should be subject to a formal verification. This will align the requirements for the marketing authorisation holder, who will enjoy the benefits of the orphan regulation, especially in terms of market exclusivity, for an extended marketing authorisation, with those required set under the orphan Regulation for another applicant seeking authorisation for a different subset of patients within the same orphan condition or a first line treatment from the onset.

Consequently, if a sponsor varies its marketing authorisation to a new subset of the condition, the variation will entail a review of the orphan criteria as far as this new subset is concerned to ascertain that the orphan marketing authorisation complies with Article 7.3. It is understood that the reviews from the Committee on Orphan Medicinal Products include whether these new therapeutic indications have a significant benefit over existing treatments and that the applicant therefore merits its status of orphan for another sub-set of the condition. If that is not the case, the applicant may have to seek a separate marketing authorisation outside the scope of the orphan legislation.

2. Separate marketing authorisation

Article 7(3) provides for the possibility that a sponsor of an orphan medicinal product can *"apply for a separate marketing authorisation for other indications outside the scope of this Regulation"*. On the other hand it is also possible that a marketing authorisation holder of a non-orphan medicinal product may 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 are handled separately from marketing authorisations for non-orphan medicinal products in order to provide legal certainty that the benefits of market exclusivity provided by the Regulation can be enforced.