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SCIENCE MEDICINES HEALTH

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Committee for Orphan Medicinal Products (COMP)

Points to consider on the estimation and reporting on the prevalence of a condition for the purpose of orphan designation

COMP guideline

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[1] Revision includes further explanation on key definition of epidemiological concepts used in designations; appropriate indices expected in several scenarios; direct and indirect methods of estimating the number of affected individuals.

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Table of contents

This document should be read in conjunction with the following regulations and guideline, which address a number of fundamental issues, such definitions of a valid condition:

- Regulation (EC) NO 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products
- Commission Regulation (EC) No 847/2000 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 definition of the concepts ‘similar medicinal product’ and ‘clinical superiority’
- European Commission Guideline on the format and contents of applications of designation as orphan medicinal product (ENTR/6283/00)
- 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)

1. Introduction

The aim of the European Regulation on orphan medicinal products is to promote the development of products for life-threatening or chronically debilitating rare diseases[2] where pharmaceutical industry would be unwilling to develop products under normal market conditions (Recital to 141/2000)[3].

Where an orphan designation application is based on the claim that a condition for which the medicinal product is intended is rare, i.e., that the condition "affects not more than 5 in 10,000 persons in the Community when the application is made", then the rarity of the condition should be demonstrated by the sponsor based on relevant epidemiological data. Alternative requirements will be defined for situations in which the epidemiological measure "prevalence of the underlying condition" is not regarded as appropriate.

No matter how rare a condition actually is, it is not sufficient to state that it is 'obviously' rare and the prevalence is far below the 5 in 10,000 limit. Generally, demonstrating that the prevalence of a condition meets the criterion will consist of a review of literature and of any reference databases together with a critical presentation of methods, result and conclusions. Where all available data show conclusively that the population prevalence of the proposed condition lies well-below the threshold at the time the application is made, the fulfilment of the prevalence criterion will be a relatively simple task. In less clear situations, careful assessment of the quality of the data and weighing of the evidence from available sources may be necessary to establish that the population prevalence lies below the threshold.

It is critical to justify that the proposed prevalence is up-to-date both at the time of initial designation, the time of review of the orphan designation at marketing authorisation or at later major variations to the marketing authorisation of the proposed product and in the course of a procedure of the review of the period of market exclusivity according to article 8(2). Each (of all) therapeutic indication(s) of an orphan medicinal product need to comply with the criteria set out in Regulation 141/2000 Article 3.

Each sponsor has to provide a prevalence estimation for each application, mere reference to prior orphan designations, even if recent, is not accepted.

It is assumed that valid epidemiological designs and statistical methods are used throughout the different steps involved in the estimation and reporting of the prevalence. The aim of this points-to-consider document is primarily to assist the sponsor in establishing the prevalence of a condition according to 141/2000.

2. Problem statement

The 'prevalence criterion', which is described in article 3 (1) (a) of Regulation (EC) No 141/2000, requires the demonstration through evidence-based references that the disease or condition for which the medicinal product is intended, affects not more than 5 in 10,000 persons in the Community, when the application is made (for definitions, see below).

In many situations, the *true* prevalence (defined as the number of persons affected by a condition at a specified instant in time in a given population) at the time of applications will not be known and the demonstration of the 'prevalence criterion' will be based on the estimated prevalence of the condition at a certain point in time. Where this is the case, there should be justification that the estimate provided is a

[2] 141/2000 Article 3 a) first paragraph
[3] 141/2000 Article 3 a) second paragraph

good approximation of the true prevalence of the claimed orphan condition in the European Union, at the time of application.

3. Key definitions

3.1. Definition of prevalence

Regulation No 141/2000 requires the demonstration that the disease or condition of which the medicinal product is intended, affects not more than 5 in 10,000 persons. However, there are different methods possible to estimate the number of persons affected by a disease.

Definitions

Prevalence is defined as the number of persons affected by a condition at a specified instant in time in a given population. It is typically reported as a proportion.

Point prevalence is the proportion of a population that is alive and affected by the specific condition at a specific point in time, typically the time of application

- Complete prevalence (also referred to as full prevalence or life prevalence) represents the number of previously diagnosed persons alive at the specific point in time regardless of how long ago the diagnosis was, or if the patients may now be considered cure or may need treatment;
- Partial prevalence limits the number of patients to those diagnosed during a fixed time in the past, e.g. 5 years.

What measure should be reported?

Adequate use of these epidemiological indices need to reflect the nature of the proposed condition, and whether the condition is acute, subacute or chronic. The choice of the specification of prevalence needs always to be explicitly justified by the applicant in section B of the application.

Complete prevelance is required for chronic diseases, in which case a patient previously diagnosed may be considered always “affected by” that condition until the time of death.

Partial prevalence may be appropriate for non-chronic diseases.

For example, to estimate the prevalence of cancer it may be difficult to define when the condition is still present and should be counted as a “prevalent cancer case”. For certain cancers, patients who are still alive after a certain number of years after diagnosis may be considered cured since the death rates of such patients are similar to those in the general population. Therefore, in this case the prevelance may be estimated best if all patients diagnosed in that period with initial disease or metastases are counted. The choice of this time period needs to be substantiated on a case to case basis, by explicitly considering the population “affected by” the proposed condition.

3.2. Established exceptions to the use of prevalence

There are situations in which the epidemiological measure “prevalence of the underlying condition” may critically underestimate the actual frequency of the clinical situation in which a medicinal product is administered. Therefore, the European Commission identified instances in which the threshold is exceptionally defined differently from point prevalence.

- Diseases of short duration, (i.e. less than a year)
  For conditions which no longer affect an individual after an acute presentation of less than a year, yearly incidence rates rather than point prevalence should be used in view of the objectives of the orphan drug legislation.

- Prevention/Diagnosis as orphan indication:
  If the product is intended for prevention or diagnosis of a condition, then the limit of 5 in 10,000 persons in the Community refers to persons receiving the preventive treatment or the diagnostic test and not those affected by the condition itself. More generally if the number of persons requiring administrations of a product for prevention or diagnosis of a condition exceeds the number of persons affected by the condition, then the estimation of fulfilment of the criterion of rarity should be based on the number of persons that are candidates for being administered the product on an annual basis.

3.3. Definition of the number of people affected (the numerator)

The starting point for any prevalence estimation is the definition of a medically plausible condition that is generally recognised by the medical community as a distinct medical entity. In the practice of the COMP, an orphan condition is usually broader than the therapeutic indication for marketing authorisation.

Guidance on how to define medically plausible conditions can be found in the European Commission *Guideline on the format and contents of applications for designations as orphan medicinal product* (ENTR6283/00).

The term “affected by” in the context of the orphan regulation, is understood as having been diagnosed with a disease according to current clinical criteria and comprehensively includes all stages or different degrees of severityof an underlying condition. If classifications have changed over time, the sponsor is to describe the impact of these changes on the estimation of prevalence of the proposed condition. For genetic diseases of low penetrance the prevalence of diagnosed patients should be established, not the allele frequency in the population at risk. For conditions with primary and secondary (or higher) forms, the prevalence of each aetiology needs to be summed up in order to provide the total prevalence of the proposed condition.

The term “affected by” also entails a dimension of time that has elapsed from a past diagnosis, which should be duly justified for each case. Details of the condition that the medicinal product is intended to diagnose, prevent or treat should be provided (natural history including stage distribution at diagnosis, causes, symptoms and prognosis). The duration of the condition should be described, if necessary by different stages. Furthermore, rates of cure, relapse or recurrence should be provided. For conditions with late relapses or with recurrent episodes, the average periods without overt signs of the diseases should be clearly stated. The information on the natural history of the disease including causes, symptoms and prognosis should provide a clear characterisation of the disease or condition in question and should be based on published references.

Subsets of conditions

For less well-defined distinct medical entities, such as subsets of recognised conditions as described in the Guideline on the format and content of applications for designation as orphan medicinal products (ENTR/628/00), insufficiently reliable data may be found. Where the sponsor claims that a subset of a condition complies with the criteria as described in ENTR/6283/00 Rev, then the application should report the prevalence and yearly incidence rate of the subset as well as that of the broader condition.

3.4. Definition of the population (the denominator)

For the purposes of orphan designation the number of persons affected in the Union should be estimated based on the entire population of the Union at the time of application. Subsetting of the population according to age or gender should not be done i.e. even if a condition occurs only in children or only in women, the entire population of the Union is taken as the denominator. Since epidemiological data are often reported only with respect to the population at risk, this may need to be highlighted and taken into account when estimating prevalence in the application.

4. General points to consider

4.1. Geographic variation

For the fulfilment of the orphan criteria, prevalence within the EU needs to be established, regardless of the number of persons affected outside the EU.

Where comprehensive prevalence data for the Community is not available, but data from individual EU Members States or other national regions is available, assumptions for extrapolating these data to the whole Community will have to be made and justified. The possibility of spatial variations may affect the prevalence of the disease and should be considered and appropriately accounted for, for example north-south difference in the prevalence of thalassaemia or differences in patterns of hospital admission for different health-care systems. If differences in demographic factors, such as age distributions, affect the prevalence estimate, these need to be accounted for if extrapolation from one or multiple countries to the EU population is necessary.

4.2. Temporal variation and time trends

It is necessary to refer to data as recent as possible in order to comply with the criterion “at the time the application is made”. The possibility of temporal variations (e.g. increasing incidence due to change in risk factors, increasing incidence due to demographic change, increasing duration of condition due to improvement in treatment outcomes) should be taken into account. The sponsor may need to provide best or worst-case scenarios for prevalence if ongoing time trends are documented.
The use of age-standardisation is explicitly not appropriate in view that it does not provide the prevalence of a condition in the population of the EU at the time of designation but that of a standard population.

4.3. Orphan condition not occurring in the EU at the time of designation

Communicable diseases 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. 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 the disease currently does not occur in the EU at all, account should be taken of the risk that persons in the EU may become affected.

4.4. Point estimates close to the statutory threshold

In case of point estimates close to the rule of beyond 5 in 10.000 it is the task of the sponsor to convince the committee that the estimate is sufficiently robust and the condition can still be considered rare in the meaning of the orphan regulation. Time trends and/or geographic variation need to be thoroughly discussed, including changes in diagnostic criteria or changes in classification. Sensitivity analyses have to be provided in which the most critical assumptions are varied.
If it cannot be convincingly demonstrated at the time of marketing approval that the theshold of less than 5 in 10,000 persons is met, the COMP may consider that on balance the threshold has been breached and that orphan designation cannot be granted.

5. Establishing the prevalence of a condition

5.1. Identification of epidemiological data

The best and most reliable sources on epidemiological data will vary depending on the condition of interest. There is no unique best source. The strategy for the identification of prevalence data should be presented together with a thorough discussion of potential biases indicating under- or overreporting, due to for example publication bias and selection bias. Standard sources of information typically consist of epidemiological and medical peer-reviewed articles, databases and registries. The source of the data and methodology should be documented. Unsubstantiated statements about the prevalence of a condition derived from a textbook, monograph or a thesis on the condition will be insufficient.

A systematic review of available literature is often sufficient for producing a reliable estimate of prevalence. However, up to date data on prevalence, especially complete point prevalence within the EU, are not readily available for all conditions. Therefore, to update the estimate of prevalence at the time of orphan designation or marking authorization, current incidence data will often have to be used to estimate prevalence. Where standard sources may have shown to be uninformative or unreliable, the sponsor should also consider to count the occurrence of the condition in admission or discharge records of hospitals and specialised centres, to survey General Practitioners, to contact rare disease or patient organisations, to use statistics on drug use or statements from experts.

In case additional relevant epidemiological studies are identified during the evaluation of the application for orphan designation, the sponsor should promptly inform the EMA if relevant new prevalence information becomes available during the designation procedure.

5.2. Validity and comparability of data

After all potentially relevant sources are identified, exploration of sources of bias is of great importance because studies often vary considerably in terms of design, definition of the condition and methodology. Such differences may induce artificial heterogeneity that needs to be distinguished from real variation of the occurrence of the condition. Methods to assess potential bias of the point estimates should be described in sufficient detail. The exclusion of individual sources or studies from the overall evaluation of prevalence should be described and substantiated. Depending on the disease, regional registries with high data quality may be preferred over pan-European registries with less granularity and spatial extrapolation may be therefore be justifiable.

5.3. Derivation of prevalence based on indirect methods

5.3.1 Epidemiological data only reported for broader populations

Frequently, no direct prevalence estimate is available for individual rare diseases but only for a group of diseases (e.g. leukaemia as such and not specified to acute lymphoblastic leukaemia). Sponsors should strive to deduce the best approximation to the prevalence proportion required for the purpose of orphan designation by indirect methods (e.g. reported proportion of specific condition within reported umbrella term, age-specific incidence and typical life expectancy with condition). Indirect estimation can then be accepted as long as appropriate methods are used,the assumptions used for the estimation are described and appropriately justified and referenced to scientific literature, and the sensitivity of prevalence estimate to these assumptions has been shown as well.

5.3.2 Relationship between incidence, duration and prevalence

Under the assumptions of stable incidence and duration of the condition, the functional relationship between point prevalence (P), incidence (I) and mean duration (D) is commonly expressed as $P = I \times D$. It follows that the definition of the duration of a condition is of particular relevance for the estimation of prevalence. A prerequisite for any valid definition of the duration of the condition lies in its ability to capture the entire course of the condition, which is particularly difficult for diseases with prognostic heterogeneity.
Where the estimation of prevalence is based on particular assumptions or estimates of the average duration of the condition, then these will be subject to scrutiny as to their validity and sensitivity analyses may need to be provided. Also, there are situations in which establishing the average duration of a condition may prove difficult such as for diseases with long disease-free intervals. The latter may still be taken into account for the estimation of the duration of the condition for the purpose of the orphan regulation. Adequate justifications should be provided in order to justify the expected duration of the condition.

5.4 Reporting of results

The epidemiological section of the application should contain sufficient detail to assess the quality of the search, the data source , and the methods of estimation used by the sponsor. The main results of the epidemiological section should be stated clearly and it is on these results that the sponsor should base the conclusive claim that the point estimate lies below 5 in10,000.More detail will generally be required when the prevalence of the disease or condition is close to the 5 in 10,000 limit. Results should be listed in a tabular format giving the most relevant information and results of each study.

It is acknowledged that a rigorous estimation of the prevalence will not always be possible and a plausible range of hypothesised values or a worst-case scenario estimation will be the only possible summary of the available data. Sensitivity analyses may be necessary with appropriate justification of the assumptions made. Any exclusion of published prevelance data must be justified.

If information from more sources is available, the sponsor may choose to combine the results of relevant available sources. Details about the statistical methods for combining the data from different studies should be provided, including methods for investigation of heterogeneity.