Orphan Drugs in the EU/EEA and UK

An orphan drug, or orphan medicinal product, is a medicine that is developed to treat a rare disease, defined as a disease affecting a relatively small number of people as a proportion of the population. In recognition of the fact that the commercial market for such medicines is small, regulators have sought to provide economic incentives for their development. In this briefing we review the major aspects of orphan drug legislation and the available incentives in the EU/EEA and UK.

Obtaining an orphan designation

An orphan designation is granted for a medicinal product following a successful application to the relevant regulatory body. In the EU/EEA, most applications are made centrally to the European Medicines Agency (EMA). In the UK, the relevant body is the Medicines and Healthcare product Regulatory Agency (MHRA).

Orphan designation in the EU/EEA

Orphan medicinal products in the EU/EEA are governed by EC Regulation No 141/2000 ("the EU Regulation"). An orphan designation can be obtained at any stage prior to filing an application for marketing authorisation (MA) of the product. Typically, EU/EEA orphan designation is applied for during clinical trials.

The criteria that must be met to qualify for orphan designation are set by Article 3(1) of the EU Regulation:

1. the medicine must be intended for the diagnosis, prevention or treatment of a condition that is life-threatening or chronically debilitating;
2. either (i) the prevalence of the condition in the EU/EEA must not be more than 5 in 10,000, or (ii) it must be unlikely that marketing of the medicine would generate sufficient returns to justify the investment needed for its development; and
3. no satisfactory method of diagnosis, prevention or treatment of the condition concerned has been authorised in the EU/EEA, or, if such a method exists, the new medicine must be of "significant benefit" to those affected by the condition.

At the EMA, applications for orphan designation are assessed by the Committee for Orphan Medicinal Products (COMP). Article 5(5) of the EU Regulation requires the Committee to provide an opinion relatively quickly, within 90 days of receipt of a valid application.

An MA authorising the product for use in the orphan condition must also be obtained from the relevant regulatory body (e.g. the EMA). Under Article 7(3) of the EU Regulation, the MA can only cover therapeutic indications that meet the "orphan" requirements (1) to (3) above. A single MA cannot cover both orphan and non-orphan conditions. If clinical data are available to support the authorisation of a single product for both orphan and non-orphan indications, separate MA applications are required.

Orphan designation in the UK

Following the withdrawal of the UK from the EU, orphan medicinal products in the UK are governed by the Human Medicines Regulation ("the UK Regulation"). Unlike the EU procedure, it is not possible to obtain an early orphan designation. Rather, the application for orphan designation in the UK must be made at the same time as the application for MA in the UK. The MHRA's advisory committee, the Commission on Human Medicines (CHM) will examine the application for orphan designation. Examination of the application for orphan designation and for the MA takes place in parallel and a decision on both will be given at the same time. As in the EU/EEA, a single MA cannot cover both orphan and non-orphan conditions.

The assessment criteria for grant of orphan designation in the UK are effectively the same as criteria (1) to (3) of the EU Regulation, with the additional requirement that for (2)(i) the prevalence of the condition must not be more than 5 in 10,000 in the UK specifically.

Additional considerations for Northern Ireland

Post Brexit, Northern Ireland continues to subject to certain EU Regulations, including with respect to medicinal products. This has implications for the grant and application of orphan status within the territory, as compared to the remainder of the UK (i.e. England, Wales and Scotland, collectively Great Britain). Specifically, EU/EEA orphan designations extend to Northern Ireland. As such, a UK-wide orphan designation will only be granted by the MHRA if no corresponding EU/EEA orphan designation exists. In that case, if an orphan designation is subsequently obtained in the EU/EEA, the holder of the orphan designation in the UK must apply to amend the orphan designation from a UK-wide designation to a designation for Great Britain only. Alternatively, if an EU/EEA orphan designation does already exist, the MHRA will grant an orphan designation for Great Britain only. In both cases, the EU/EEA orphan designation will determine the status of the product in Northern Ireland.

Incentives for orphan designation

Market exclusivity

The EU/EEA and UK provide similar rewards for orphan designation, the main such reward being a period of 10 years market exclusivity for the product from the date of the orphan MA (Article 8(1) of the EU Regulation, Article 58(D)(1) of the UK Regulation).

During this 10 year period no third party can launch **any similar product**[1] on the market, even if the third party generates their own clinical data and even if the third party product is not structurally identical to the authorised orphan product. If more than one orphan designation is obtained for the same medicinal product, such that there are separate MAs, a separate 10 year

market exclusivity period is available for each orphan designation, starting from the date of the relevant MA.

Significantly, the exclusivity period in the UK is defined as "up to" 10 years. This is because the period will run from the date of the **first** EU/EEA **or** UK MA for the orphan designation. Thus if the EU/EEA MA for the product is granted first, the exclusivity period based on the UK authorisation (covering Great Britain) will be reduced accordingly. The intent is to encourage applications for orphan designation in the UK as early as possible. However, in the reverse situation, (the UK authorisation is first) the exclusivity period in Northern Ireland (driven by the EU/EEA MA) will expire later than in the rest of the UK.

The marketing exclusivity period in the EU/EEA and UK is also subject to some exceptions. Specifically, a similar product may be marketed within the period if:

i. the holder of the MA for the original orphan product gives consent to a subsequent applicant;

ii. the holder of the MA for the original orphan product is unable to supply sufficient quantities of the product; or

iii. the subsequent applicant can establish that its product, although similar to the orphan product already authorised, is safer, more effective, or otherwise clinically superior.

Other incentives

Other rewards for orphan designation in the EU/EEA include specific advice and assistance provided at a reduced charge to aid with the marketing authorisation process, as well as certain marketing authorisation fee reductions. There are also various grants and funding incentives for the development of orphan drugs available via the European Commission. The UK offers similar marketing authorisation fee reductions.

Additional incentives for paediatric indications

The EU/EEA and UK both offer an additional incentive to invest in the development of medicines for orphan indications in children. On completion of a pre-agreed paediatric investigation plan (PIP) for an orphan medicine, the 10 year market exclusivity period will be extended by 2 years to a total of 12 years from the initial orphan authorisation.

A paediatric authorisation of the medicine does not need to be granted for the 2 year extension to be obtained. Rather, the reward is granted for carrying out the paediatric clinical studies. To obtain the extension, the paediatric studies must be completed prior to the expiry of the initial 10 year market exclusivity period. A practical implication of this is that the PIP must be completed in sufficient time before the expiry of the 10 year period to allow the necessary changes to the MA and the summary of medicinal product characteristics (SmPC) to be made. It is a requirement for grant of the extension that the MA and SmPC be updated to reflect the results of the paediatric studies.

Orphan medicinal products are not eligible for other paediatric development rewards in the UK and EU/EEA countries,[2] notably the 6 month extension to the term of an SPC that may be available upon completion of an agreed PIP. However, under certain circumstances it may still be possible to choose the preferred reward – see the following section.

For further information on paediatric medicines in the EU/EEA and UK, please see our separate briefing on this topic.

Revocation of orphan designation

An orphan designation and the associated rewards may be revoked if a medicinal product no longer fulfils the orphan criteria (1) to (3).

Both the EU and UK regulations provide for an explicit review at the end of the 5th year of the 10 year market exclusivity period. If the relevant regulatory authority is no longer satisfied that the orphan criteria are met, the 10 year market exclusivity period is reduced to a 6 year period (i.e. the last 4 years of market exclusivity are lost).

In the EU/EEA it is possible for the sponsor/MA holder to request revocation of an orphan designation. This may be desirable if the term of protection provided by an SPC + 6 month paediatric extension may exceed the term provided by the 10 year marketing exclusivity period + 2 year paediatric extension. As indicted above, the 6 month SPC extension is not available for a designated orphan product, but it can be pursued after the orphan designation is withdrawn, provided that the withdrawal takes place before the end of the 10th year of the marketing exclusivity period.[3]

The relationship between orphan rewards and standard data exclusivity periods

The 10 year market exclusivity period for orphan medicines runs in parallel with the standard periods of data exclusivity and market protection that are available for all newly authorised medicines. For further information on data exclusivity and market protection in the EU/EEA and UK, please see our separate briefing on this topic.

Summary

Both EU/EEA and UK law provide significant incentives to develop medicinal products for orphan diseases. In particular, each orphan designation is rewarded with 10 years of market exclusivity from the date of first marketing authorisation in the EU/EEA or UK for the relevant condition. The period can be extended to 12 years if an approved paediatric investigation plan is carried out. Competitors are prevented from launching similar products for the duration of the exclusivity period.

The orphan rewards run in parallel to patent and SPC protection, and standard data exclusivity and market protection. For medicinal products that take a long time to devesimilarlop and bring to market, such that there is only a short time remaining on underlying patents or SPCs, the orphan market exclusivity provisions can be particularly valuable.

Footnotes

1. A "similar" medicinal product is defined as a product (a) containing a similar active substance, i.e. a substance which is identical or which has the same principal molecular structural features and which acts via the same mechanism, and (b) which is intended for the same therapeutic indication (see Article 3 of EC Regulation No 847/2000).
2. This does not include Switzerland, which is a not an EU/EEA member. Switzerland operates comparable rewards for orphan designations and a comparable SPC system to the EU/EEA and UK, but at present has no prohibition in law to prevent obtaining both forms of paediatric reward for an orphan drug.
3. This practice was endorsed in 2020 by the District Court of The Hague in decision C/09/595262 KG ZA 20-605 *(Novartis v*

Mylan). Novartis revoked the orphan designation of Exjade (deferasirox) in order to pursue a 6 month extension of their SPC. Whilst not binding on other EU/EEA member states, there is currently no reason to expect other national courts to diverge from this interpretation of the relevant legislation.

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