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Demonstrating Significant Benefit For Orphan Medicines - Is It Time For A Drastic Change?

By Geneviève Michaux, 8 June 2016

As the European Commission explores how to streamline its rules governing orphan medicines, Geneviève Michaux examines where the weaknesses in the system lie and how to fix them.

The EU’s Orphan Regulation has undoubtedly been a success. Over the past 16 years, more than 1,500 orphan designations have been granted under the legislation - which was adopted in December 1999 to promote the development of medicinal products for rare diseases - and more than 100 orphan medicinal products have been approved. However, as the “second generation” of orphan products arrives and with more companies becoming involved in the rare diseases area, the EU’s orphan system has begun to show its limitations.

A key failing of the orphan system concerns one of the two cornerstones of the Orphan Regulation: orphan designation (OD). Specifically, sponsors are required to maintain the OD that they received during their product’s development by producing scientific evidence to support the OD criteria when they apply for marketing authorization (MA). Producing the scientific evidence of significant benefit can be (very) challenging. If sponsors fail to maintain the OD, they cannot benefit from the 10 years of market exclusivity that is available under the Orphan Regulation to allow companies to recoup their investment in rare diseases – which is the other cornerstone of the regulation. The possibility of losing OD during the MA procedure undermines the predictability of return on investment on which the orphan regime is based.

Despite the regulation’s success, there are still many rare diseases for which drugs need to be developed. As such, the orphan regime must remain attractive, in particular for SMES, which are the most active group in this area.

The European Commission is currently reviewing its 2003 Communication on orphan medicinal products in a bid “to streamline the regulatory framework and to adapt the communication to technical progress.”

In the meantime, this article examines the concept of significant benefit, its application, the problems it introduces and how these might be addressed. It also explores the discrepancies with provisions of the Orphan Regulation that do not require sponsors to substantiate systematically the maintenance of the OD criteria at the time of the MA; and the requirement, in certain cases, to provide unattainable evidence. Finally, it proposes a number of solutions to improve the designation system in a way that does not impede the objectives of the Orphan Regulation.

For example, the commission could abandon the automatic review of the OD criteria at the time of the MA and replace it with a reduction of market exclusivity, which is the measure expressly set forth by the Orphan Regulation to ensure the maintenance of the OD criteria. Alternatively, the comparison with authorized medicinal products could be limited or facilitated. Such changes might be considered drastic, but they would not only bring the OD system closer to the one envisaged by the Orphan Regulation but also secure the continued success of the regulation as the number of orphan medicinal products continues to grow.

**Orphan Designation In The Orphan Regulation**

The OD criteria and the OD procedure are covered by the Orphan Regulation (Regulation (EC) No 141/2000) and the evidence required is covered by guidelines from the commission.

The regulation contains two articles on OD: Article 3 establishes the criteria for OD and Article 5 sets forth the procedure for OD.
Pursuant to Article 3, to qualify for OD, a medicine must meet three criteria: (a) the disease must be life-threatening or debilitating or serious and chronic; (b) the prevalence of the disease must be low (epidemiological criterion) or the return on investment from marketing the product is unlikely to be sufficient (economic criterion); and (c) no satisfactory authorized treatments should already exist, or if they do, then the medicine must show a significant benefit over any authorized existing treatments (medical criterion).

Interestingly, even though the European orphan system was supposed to be modeled on the US and Japanese orphan regimes, the last two do not impose a medical criterion.

Article 5 specifies that the sponsor must file the application for OD before submitting the MA application (MAA), and provides a few rules on the content of the OD application and the procedure for OD, which involves an opinion from the European Medicines Agency’s Committee for Orphan Medicinal Products and a decision from the commission.

Once the OD is granted, the medicinal product is recorded in the Community Register of Orphan Medicinal Products. Pursuant to Article 5(12), it is removed from the Register:

(a) at the request of the sponsor; (b) 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; (c) at the end of the period of market exclusivity as laid down in Article 8.

**Orphan Designation As Implemented By The Commission**

**Definition of Significant Benefit**

Commission Regulation (EC) No 847/2000, which implements the OD criteria, provides several legal definitions, including the following for significant benefit: “a clinically relevant advantage or a major contribution to patient care.”

The commission’s 2003 Communication on orphan medicinal products further interprets and clarifies the Orphan Regulation. The Communication gives examples of significant benefits, such as expected benefits to a particular population subset, including benefits to patients resistant to existing methods; more favorable and clinically relevant pharmacokinetic properties; a more convenient formulation or route of administration; expectations of a clinically relevant improved safety profile; increased availability; etc.

The concept of significant benefit is different from the concept of clinical superiority used in Article 8 of the Orphan Regulation. Regulation 847/2000 defines clinically superior as:

*a significant therapeutic or diagnostic advantage over and above that provided by an authorised orphan medicinal product in one or more of the following ways: (1) greater efficacy [...]; or (2) greater safety in a substantial portion of the target population(s) [...]; or (3) in exceptional cases, [...] a major contribution to diagnosis or to patient care.*

Clinical superiority was the criterion initially used in Article 3 when the Orphan Regulation was being drafted. It was replaced by significant benefit during the legislative process on the grounds that clinical superiority is difficult to prove at the early development stage, when the designation is likely to take place. The OD should be granted in cases where the second product is better although not clinically superior to the first medicinal product. In practice, however, the COMP’s increasing demands with regard to the demonstration of significant benefit, seems to bring surreptitiously the two concepts closer.

**Evidence of Significant Benefit**

Regulation 847/2000 sets out specific rules on OD criteria and their evidence. In particular, it determines the documents that must be submitted in order to support the epidemiological and economic criteria. By contrast, the regulation does not specify the evidence requirements for the medical criterion, which are instead included in guidelines.

In the 2010 case of Novo Pharm v European Commission, the General Court ruled that “[e]stablishing significant benefit therefore takes place in the context of a comparison with an existing authorised medicinal product or method. The clinically relevant advantage or major contribution to patient care can be established by comparison with treatments that have already been authorised.” The commission expects such a comparison to be made with, and the significant benefit to be demonstrated over, any competitor medicinal product approved in the EEA, at the national or Union level. Off-label use, however, need not to be taken into account.
The commission’s Communication sets forth a two-step designation, i.e., orphan designation is granted during development and then it must be maintained later on at the time of the MA application. The means of proving the medical criterion – i.e., significant benefit – varies depending on the step.

At the time of designation, significant benefit may be based on assumptions because little or no clinical experience is available at that time. The assumptions have to be well justified, i.e., plausible, based on sound pharmacological principles, with preclinical and preliminary clinical data as supportive evidence⁸.

At the time of the MA procedure, the orphan status is reviewed to ensure that the OD criteria are still met. The commission has interpreted Article 5(12)(b) as “meaning that the criteria for OD shall be reviewed before a MA is granted” (emphasis added)⁹. At that point in time, a higher level of data/evidence is required, and the significant benefit has to be demonstrated with comparative data. The EMA’s recommendation on medical plausibility and significant benefit adds specifications, such as that “[t]he COMP will evaluate whether there is a high probability for the patients to experience a clinically relevant benefit. Thus, it has to be concrete and based on the data contained in the [MA application]” or on the collaboration between the COMP and CHMP to ensure consistency¹⁰. The recommendation also clarifies that “[i]t is expected that most of the data […] will be generated during the clinical development of the product. [...] Any advantage will be considered in the context of experience with authorised products in the orphan condition even if comparative clinical studies are not always required or possible.”

The COMP’s review of the OD occurs after the adoption of the CHMP opinion as the COMP has to determine whether the therapeutic indication agreed by the CHMP falls within the orphan indication. Indeed, in the commission’s OD system, the designation covers an orphan indication (treatment, diagnosis, prevention of a rare disease) that may be broader than the therapeutic indication to be authorized for the medicinal product. In practice, this is almost always the case, which results in a disconnect between the scope of the OD and the scope of the market exclusivity (market exclusivity is limited to the therapeutic indication).

According to the commission, the review of the OD criteria triggers the same procedure as the OD procedure. The evidence has to be included in a report on the maintenance of the OD criteria to be submitted to the EMA in parallel with the MAA¹¹.

If the orphan status is lost, the medicinal product will no longer benefit from market exclusivity, but the EMA does not recover the other incentives that the sponsor might have received beforehand, such as protocol assistance.

Protocol Assistance
The commission and the EMA “highly” recommend that sponsors make use of protocol assistance, especially with regard to demonstrating significant benefit over authorized medicinal products. In practice, the EMA provides combined advice from its Scientific Advice Working Party and the COMP and if protocol assistance is not followed, the sponsor is asked to justify the deviation.

Problems With The Current Orphan Designation System
As mentioned above, the OD is granted on the basis of well justified assumptions and maintained at the time of the MA procedure on the basis of comparative data in light of all authorized competitor medicinal products. The commission instituted this two-step designation system because while it considers that significant benefit must be demonstrated by comparative data, it recognizes that such data is only available when the sponsor is ready to submit the MAA and that the granting of OD early in the development process is very important to sponsors, especially SMEs.

Yet, this two-step system raises issues. First, it carries the risk of losing the orphan status right before obtaining the MA, which conflicts with the rationale and objectives of the Orphan Regulation and may ultimately undermine it. It also is not fully in line with the Orphan Regulation. Finally, in certain cases, sponsors may be, de facto, asked to bring unattainable evidence.

Undermining The Regulation
The loss of the OD during the MA procedure means that the approved medicinal product will not benefit from market exclusivity and that the sponsor thus will not be
able to recoup its investment as it had expected. The situation is even worse for old active substances that are “repurposed” for a new orphan indication because the new R&D data are not protected by data exclusivity (or at most they are protected for one year, depending on the circumstances). In such cases, the sponsor may only protect its (expensive) data by withdrawing its MAA, which is obviously not in the interest of patients.

Conflicting With The Regulation’s Objectives And Rationale

The Orphan Regulation presupposes that companies will want to invest in rare diseases because they know they will recoup their investment thanks to market exclusivity. The objectives of the Orphan Regulation therefore are to improve the availability of orphan medicinal products and to ensure appropriate and effective incentives for R&D in rare diseases. Recital (8) of the regulation illustrates that market exclusivity is key to incentivize research in, and marketing of, orphan medicinal products:

[…] the strongest incentive for industry to invest in the development and marketing of orphan medicinal products is where there is a prospect of obtaining market exclusivity for a certain number of years during which part of the investment might be recovered [...].

While the orphan status gives sponsors important advantages that remain despite the loss of OD, market exclusivity remains the biggest incentive that the Orphan Regulation offers.

The current system is unfair as sponsors invest in rare diseases in the belief that they will benefit from the advantages of the Orphan Regulation and they only learn that they will not after having made the investment. In other words, the two-step approach to OD creates unpredictability about market exclusivity and thus return on investment.

The unpredictability stems mainly from the medical criterion. The problem with the medical criterion is that it is based on a comparison with medicinal products that the sponsor might not anticipate will be authorized – at the national or EU level – in the period between its OD and MAA. Also, the sponsor might not know how those newly authorized medicinal products will relate to its product. The medical criterion is, therefore, the weakest link in the orphan system, especially its “significant benefit” component, as more than 70% of the ODs are based on significant benefit. Moreover, the increasing number of orphan products being developed in certain therapeutic areas will feed this weakness as the more competitor products there are, the more likely the OD will not be maintained at the time of the MA.

The lack of predictability negates the objectives and rationale of the Orphan Regulation and, as such, may deter companies from investing in the development of orphan medicinal products and ultimately undermine the Orphan Regulation.

Automatic Review Of OD Not Envisaged by Regulation

An automatic review of the OD criteria at the time of MA is not part of the OD system envisaged by the European legislature. None of the legislative documents mentions an automatic review. The commission did not even include the possibility of removing the OD before MA in its explanatory memorandum when the legislation was being drafted; this was added by the Council of the European Union during the legislative process for reasons which remain unclear.

The possibility of removing the OD before MA was not meant to create, or result in, an automatic review of all the ODs, and it clearly results from the Communication that the automatic review of the OD criteria is the Commission’s own – and stretched – interpretation of Article 5(12).

In the system envisaged by the legislature, once granted, the OD was meant to remain, and the review of the OD criteria before MA was supposed to be the exception rather than the rule as doing so jeopardizes the incentive that anchors and balances the Orphan Regulation. The mechanism that was foreseen to ensure that medicinal products continue to deserve benefiting from the orphan incentives, is the reduction of market exclusivity. One wonders why the commission did not simply rely on the reduction of market exclusivity, which is expressly set forth by the Orphan Regulation.

Burden of Proof

The Commission and the EMA have implemented a system in which the sponsor must request and substantiate the maintenance of the OD. However, Article 5 (12) of the Orphan Regulation concerns not the maintenance of the OD but the non-fulfillment of the OD criteria and, as such, it logically does not place the burden
of proof on the sponsor as Article 3 (1) expressly does. Pursuant to Article 5(12), the OD is 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 [...]” (emphasis added).

Interestingly, a similar wording is used in Article 8(2) on the reduction of the market exclusivity:

This period may however be reduced to six years if, at the end of the fifth year, it is established, in respect of the medicinal product concerned, that the criteria laid down in Article 3 are no longer met [...] (emphasis added).

Under the commission’s guideline implementing this article, the burden of proof is not on the MA holder but on the EU member state: the member state that initiates the reduction procedure must provide the rationale for its doubts and include appropriate data justifying why at least one criterion is no longer met. The MA holder has to provide a critical review of the maintenance of the OD criteria but does not have to demonstrate significant benefit over “new” medicinal products, i.e., those approved since the granting of the MA.

In addition, the guideline says that:

[If the available evidence is insufficient to establish with reasonable confidence whether or not the designation criteria continue to be met, COMP will recommend that the period of market exclusivity is not reduced.]

The single case in which the COMP has given an opinion on the reduction of market exclusivity suggests that reasonable requirements on evidence are placed on the MA holder (the COMP gave a negative opinion on the reduction of the market exclusivity for Plenadren, which had been requested by the UK).

Again, one wonders about the reasons for applying such different evidence standards at five year intervals (i.e., at the time of MA and at the time of review of the OD criteria).

Unattainable Evidence
In certain cases, the commission’s requirement for sponsors to demonstrate significant benefit conflicts with the rules on evidence established by national courts and the Court of Justice of the European Union. At the time of the MA, significant benefit has to be demonstrated by comparative data. The commission/COMP generally require direct comparative data and only agree to indirect comparisons (meta-analysis, registries, etc.) in exceptional circumstances.

The conduct of comparative trials is not much of a problem when the competitor medicinal product(s) has been authorized for several years. In such cases, the real issues concern the limited patient population, the added investment in the “development” of the medical product and the identification of the legitimate comparator, i.e., the medicinal product likely to be used as reference by the CHMP (the comparative trial is usually required in relation to the evidence of a positive risk-benefit balance), the COMP and the health technology assessment (HTA) bodies.

The situation becomes more complex when a competitor medicinal product is being assessed for approval at the same time as medicinal product of the sponsor or has been approved only one or two years before. While this situation remains rare, it will undoubtedly occur more frequently in the future.

When two medicinal products start the MA procedure at the same time (or more or less at the same time), the sponsor of the second product cannot demonstrate significant benefit over the first product by comparative data, be it indirect, because the sponsor does not have access to the first medicinal product itself or to any relevant data thereon. And this lack of access lasts at least until the first product is actually placed on the market, which may sometimes take years in the case of an orphan product (due to pricing and/or reimbursement procedures).

The situation is usually – but not always – better when the first product has been approved one or two years earlier.

It is certainly better when the two products have different safety profiles or clearly different characteristics. But if they do not, demonstrating significant benefit becomes challenging.

Typically, a sponsor closes its last clinical trials six to twelve months before filing its MAA. Those trials do not
compare the product with the (first) medicinal product, at that time, it is not available on the market or even authorized. In such situations, the sponsor has two choices:

i. wait for the first medicinal product to be placed on the market before generating substantial indirect or even direct data and, therefore, delay substantially the MA procedure for its own medicinal product, invest even more in the product and risk off-label use; or

ii. immediately generate as much comparative data as is reasonably possible at that time given the lack of experience with, or even the unavailability of, the first product and, as such, reduce the delay in its own MA procedure but lose the OD because significant benefit is not demonstrated by the means of the proof required by the COMP.

Fortunately, the sponsor may ask the EMA for protocol assistance with regard to significant benefit, but the SAWP/COMP has to agree on a means of proof that is manageable at the time. Moreover, the COMP has to accept the SAWP/COMP advice, which it should do as all the guidelines strongly encourage sponsors to seek protocol assistance, and as such, imply that significant benefit is demonstrated if the sponsor complies with the advice.

Regardless of whether the products are assessed at the same time or are approved one or two years apart, the sponsor of the second product will lose its OD because the evidence of significant benefit that satisfies the COMP is simply impossible to provide. On the other hand, case law from the national courts and the CJEU commonly states that the exercise of a right may not be subject to evidence that is impossible to obtain, and the same should apply to the maintenance of a right, especially when the loss of the right automatically leads to a significant delay in the approval of a medicinal product for a rare disease. Consequently, the COMP should tailor the means of proof of significant benefit to each case in order to ensure that unattainable proof is not required, and limit the proof requirement to the evidence which is reasonably available at the time.

The commission created a two-step OD system to relieve the tension between, on one hand, the granting of the OD early on in the development of the medicinal product and, on the other hand, the requirement to establish significant benefit over approved medicinal products. Obviously, sponsors cannot be expected to provide scientific evidence of significant benefit at the time when the OD is granted. Yet, predictability is essential for the continuing success of the orphan regime.

Until recently, predictability had not really been a problem and ODs were usually maintained at the time of MA. The problem has arisen because an increasing number of orphan medicines are being approved for the same therapeutic areas and big pharma is becoming more involved in rare diseases, thus rendering the demonstration of significant benefit much more difficult.

Now, how to resolve this situation?

**In The Right Direction But Not Far Enough**

In November 2015, the commission started revising its 2003 Communication, which, when finalized, will be published as a “notice”; the commission expects to publish the final notice after the summer. The draft version of the notice confirms that the OD procedure is divided into two phases, and refers to the spirit of the Orphan Regulation to stress the investment in R&D for bringing meaningful advantages to patients and the necessary strictness of the OD criteria.

With regard to the maintenance of the orphan status, the draft notice specifies that:

i. direct or, when this is not possible, indirect comparative trials with an authorized medicinal product are required; and

ii. in exceptional cases, where it is not possible to generate a sample size big enough to provide statistically comparative evidence or because there are heterogeneous patient populations, it is possible to adapt clinical trial designs and alternative methods (such as indirect comparative data, historical data).

The draft notice also stresses that significant benefit does not need to be shown where two MA procedures for the same condition are running in parallel and the two MAAs are validated and assessed by the CHMP at the same time. The data are, however, required when the positive CHMP opinion for the second product is delivered after two or more CHMP meetings have taken
place for the first product. In other words, one CHMP meeting between the two assessments (i.e., a period of one month) exempts the sponsor from demonstrating the evidence of significant benefit.

Recent opinions by the COMP show that the committee has taken the same path as the commission in terms of being more flexible, at least in specific cases, and this has been confirmed by the EMA.

It should be noted that, while the COMP relaxes the means of evidence in cases of simultaneous or close MA procedures, it generally becomes more demanding regarding the evidence of significant benefit. Indeed, in cases of major contribution to patient care, the COMP now requires data to substantiate better compliance to treatment or quality of life. With regard to clinically relevant advantages, the COMP recently decided that due to parallel import, a centralized MA was not a significant benefit over a few national MAs, although the Communication lists increased availability through EU MA as an example of significant benefit.

While both the commission and the COMP are moving in the right direction, they are not going far enough, at least with regard to the increasing number of cases where two products are assessed by the CHMP at more or less the same time. One month is clearly not sufficient to allow a company to generate conclusive comparative data, even if the data are indirect.

**Big And Small Solutions**

As already stated in this article, the commission’s dual goal of granting ODs early on in the development process and ensuring that scientific evidence supports the OD criteria later on leads to unpredictability. Solutions must be found that restore the predictability envisaged by the European legislature or that, at the very least, reduce as much as possible the risk of losing the OD during the MA procedure.

At the same time, these solutions should not prevent ODs from being granted early on in product development, as this is clearly foreseen by the Orphan Regulation and it brings various advantages to sponsors, such as access to the (early) benefits of the orphan regime or funding and investments.

It is clear that providing scientific evidence of significant benefit at the time of the granting of the OD is not an option. In addition, a comparison with competitor product(s) cannot be avoided as this would conflict with the decision of the CJEU in the Now Pharm case. Within those boundaries, several solutions are available. For example:

- The two-step approach could simply be abandoned. The significant benefit would only be established by well justified assumptions, and the commission would rely on the reduction of the market exclusivity to ensure the “maintenance” of the OD criteria. This system seems to be closer to the one envisaged by the Orphan Regulation.

- The review of the OD criteria could operate along the same lines as the reduction of the market exclusivity, i.e., the review would no longer be automatic but be triggered by the EMA, the commission or a member state (possibly further to the CHMP assessment), and the burden of proof would, for a large part, be shifted to the authorities as suggested by the wording of Article 5(12).

- The significant benefit could be demonstrated by means other than comparative data. The commission/COMP could accept assumptions, a set of circumstances, compliance with protocol assistance, etc. Again, the commission would rely on the reduction of market exclusivity to ensure the “maintenance” of the OD criteria.

- The concept of satisfactory methods of treatment could refer to medicinal products that are authorized and are actually placed on at least one national market. The wording of Article 3(1) (b) is broad enough to support such an interpretation, which would make more sense in a system where comparative data is required. This solution may not cover all cases but certainly most of them.

These solutions can apply to all cases or be limited to the specific cases mentioned above (simultaneous or close MA procedures), depending on the breadth of changes the commission is willing to make to the system. If the solution has to be limited to specific cases, the first step would be to determine objective param-
eters for those cases. How many months or years would there need to be between the MA of the first medicinal product and the maintenance report for the second medicinal product? Perhaps a period of time is not the appropriate criterion, and it would make more sense to distinguish between situations, i.e., two products assessed more or less at the same time versus one or more competitor products approved after completion of the pivotal clinical trial(s). For those specific cases, additional solutions could be adopted:

- The submission of the MAA could be the cut-off date for the comparison with the authorized medicinal products. This solution would be in line with the commission’s guideline on the reduction of market exclusivity, which does not expect sponsors to prove significant benefit over the products authorized after the granting of the MA.

- The EMA itself could compare data as it holds the data on the first medicinal product (which is confidential and cannot be accessed by the sponsor of the second medicinal product). However, this raises the issue of the sponsor’s procedural rights as it would not be able to refute the EMA’s arguments.

- The sponsor of the second product could establish significant benefit at a later stage but within a reasonable deadline and, meanwhile, the medicinal product would benefit from market exclusivity. This would, in practice, create a sort of conditional significant benefit, though the commission has not shown much enthusiasm for such a move.

The rules on evidence of significant benefit could also be made more precise in order to increase predictability with regard to the demonstration of significant benefit. Doing so is as important as the rules themselves, especially as the lack of clear and precise rules on evidence gives the regulator a higher degree of discretion and thereby creates a risk of “political” decisions.

For example, the similarity between significant benefit and relative effectiveness assessment creates a risk of a political decision. HTA assessment is at the heart of many discussions, especially for orphan medicinal products given their (usually) high prices. Any temptation to deny significant benefit so as to prevent an expensive product from being marketed and subsequently receiving national reimbursement should be avoided. Currently, pricing and reimbursement is not in the EU’s remit, and significant benefit may not be seen or used as a “pre” relative effectiveness assessment.

Another risk comes from confusion over the objective of the Orphan Regulation. The draft notice makes a link between strict OD criteria and innovation, which suggests that the assessment of significant benefit should be determined by innovation. The regulation, however, has not been designed to promote innovation but the availability of the orphan medicinal products, which explains why it also applies to new orphan indications of old active substances or why a major contribution to patient care, such as an easier route of administration, is considered a significant benefit. For rare diseases, the medical criterion is the measure – and the limit – of innovation. Consequently, the number of products already approved for the same orphan indication may not matter for granting or maintaining OD as long as the new product brings a significant benefit.

References


7. Now Pharm, T-74/08, § 43, CJEU, Sept. 9, 2010


9. See Reference 5


14. British American Tobacco Intl, C-435/03, CJEU, July 14, 2005; Dilexport, C-343/96, CJEU, Feb. 9, 1999; San Giorgio, C-199/82, CJEU, Nov. 9, 1983

15. Demonstrating the significant benefit of orphan medicines, TOPRA, Regulatory Rapporteur, Vol. 163, No 4, April 2016

16. See for example the COMP opinion on the maintenance of the OD for Elocta (efmorocotocog alfa), minutes of COMP meeting October 2015, hwww.ema.europa.eu/docs/en_GB/document_library/Minutes/2015/11/WC500197139.pdf