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EU And US Orphan Drug Regimes: Benefits And Limitations Of International Cooperation

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Executive Summary

Daniel Kracov and Jackie Mulryne analyze the differences in data requirements for the authorization of orphan medicines in the EU and the US and the challenges they pose for global drug development.

EU AND US DRUG REGULATORS HAVE BEEN WORKING TO IMPROVE THEIR COOPERATION ON ORPHAN PRODUCTS

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Orphan medicines legislation in the EU and the US is similar and the regulators on both sides of the Atlantic have for some time been taking steps to improve their cooperation on drugs being developed for rare diseases so that patients can access them faster.

Nevertheless, differences between the two regions remain in terms of terminology, regulatory requirements and assessment criteria for orphan medicines. These differences can create challenges for companies striving to globalize their drug development.

About The Authors

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Ultimately, they can lead to delays in patients with rare diseases receiving life-saving drugs, and differences in terms of the authorized indications and the timing of authorization on both sides of the Atlantic.

The risk of drug delay is particularly great in the EU, as companies often choose to follow the scientific advice and requirements of the US Food and Drug Administration, given the larger market opportunity in the US compared with the EU. Following the FDA's advice and rules means the data generated might not be acceptable to the European Medicines Agency.

In this article, we discuss the current position on orphan medicines in the EU and the US, and the extent and limitations of cooperation by the regulators in both regions, in particular focusing on the data required for orphan status and marketing authorization.

Strain On Companies

It has been widely reported that medicines are becoming more personalized, targeting increasingly limited numbers of patients. Many are also targeting rare diseases, where only a small number of people are potential patients. Coupled with this, national health care budgets are tightening, meaning companies have to show real value for the medicines they develop, and it is uncertain whether health care systems around the world will be able to pay for increasingly specialized products. This all puts a strain on companies and regulatory systems, including the ability to generate sufficient data and to assess the value of those data.

As a result, there is a greater need for companies to globalize the development and commercialization of their products. This in turn leads to challenges on regulatory systems to work together to ensure effective oversight of the supply chain and the efficient exchange of regulatory and scientific expertise and information.

Two Orphan Regimes

The European authorities have long recognized that some conditions occur so infrequently that the cost of developing and bringing a treatment to market may not be recovered once the product has been launched. Therefore, the EU Orphan Regulation ((EC) No 141/2000) provides incentives and rewards for the development of orphan drugs on the basis that "patients suffering from rare conditions should be entitled to the same level of treatment as other patients." Under this regime, designation as an orphan medicinal product is critical and is based on how rare the disease is in the EU and, in most cases, the availability of other treatments for that disease (an orphan disease is deemed to be a condition that does not affect more than 5 in 10,000 people in the EU).

Receiving this designation will enable the company to access a range of advice services from the EMA, have its product automatically assessed through the EU's centralized procedure, and pay reduced fees. If orphan designation is confirmed when the marketing authorization is granted, the product will benefit from ten years of market exclusivity, which will generally protect it from competition from similar medicines for similar indications (although certain exceptions apply).

A similar regime applies in the US. Here, a company must first ask the FDA to designate its product as a drug for a rare disease or condition, which means any disease or condition that: (i) affects less than 200,000 persons in the US or (ii) affects more than 200,000 persons where there is no reasonable expectation that the cost of developing and making the drug available in the US for such a disease or condition will be recovered from sales of the drug in the US.

When a product is approved for the designated indication, orphan drug exclusivity generally bars the FDA from approving another applicant's marketing application for the same drug for the same use or indication for seven years from the date of approval (although again, certain exceptions apply).

Extent Of International Cooperation

Given the global nature of drug development, cooperation among regulatory authorities is essential to avoid duplication of work and ensure that products are approved quickly and efficiently. This is particularly the case for orphan products, which are often for the treatment of serious and life-limiting diseases and where there may be few, if any, alternative treatments. There are a number of initiatives under which the EMA and the FDA work together in this area, for example:

The EMA and FDA have had confidentiality arrangements in place since 2003, allowing for the exchange of confidential information on, among other things, orphan designation. A mutual recognition agreement (MRA) on good manufacturing practices (GMPs), entered into force between the EU and the US on 1 November 2017. Under the MRA, the two agencies can rely on each other's GMP inspection results; any additional planned inspections can be carried out based on risk, and certain requirements may be waived.

The EMA and the FDA hold regular meetings by phone or videoconference in so-called "clusters," one of which covers orphan medicinal products. This was established in 2008 to collaborate on orphan designation, product development and administrative simplification. The meetings, which are chaired alternately by EMA and FDA officials, include discussion of topics such as trial endpoints and designs suitable for small populations, areas of potential regulatory flexibility, evaluation of preclinical data to support human trials, and design and conduct of post-marketing studies. As part of this effort, the cluster has developed common procedures for applying for orphan designation and for submitting annual reports on the status of the development of given orphan medicines.

International Cooperation Limitations

Cooperation between the EMA and the FDA is largely meeting its aims but there is still room for improvement when it comes to orphan drugs.

As noted in a recent analysis by EU and US regulators, there is a high degree of alignment in marketing authorization decisions, with the agencies aligned in more than 90% of cases. The main areas where they had different outcomes were conclusions about efficacy and differences in clinical data submitted in support of an application.

Despite the level of alignment noted above, the authors of the analysis explicitly stated that because of differences in EMA and FDA regulations, they did not compare application characteristics related to orphan designation.

Indeed, it is our experience that there are more differences in opinions between the agencies for orphan products than for non-orphan products.

Further, this is an area where guidance is not consistently applied by the regulators, and the authorities have a great deal of discretion in how to approach the assessment of each product.

EMA And FDA Claim 'High Concordance' In Approval Decisions

By Neena Brizmohun

19 Aug 2019

Divergences between the EU and US agencies in marketing application approval decisions in 2014-2016 were primarily due to differences in the regulators' conclusions about efficacy based on review of the same data or to differing clinical data submitted to support the application, a study has revealed.

Read the full article here ›

We set out below some of the areas where particular differences between the EMA and the FDA have led to difficulties for companies.

Clinical Trials For Orphan Products

In both the EU and the US, the standards for the data required to obtain an authorization for an orphan product, in terms of quality, safety and efficacy requirements, are the same as for other products. As such, clinical trials of orphan drugs must be conducted to generate data on safety and efficacy of the product in the target disease area.

However, in practice, the agencies often show significant flexibility in interpreting approval standards and requirements for orphan products given the small patient populations involved and the lack of alternative options for patients. Nevertheless, a key difficulty for companies developing orphan products is designing and running clinical trials to generate sufficient data in a small disease population.

While randomized controlled trials (RCTs) are still viewed by the regulatory authorities as the gold standard for clinical research, they are not always feasible where there are few patients. Further, significant differences between trial subjects and the varying progression of certain rare diseases could impact the power of the study. Therefore, there is often a need to conduct trials for orphan products on a global basis so the company can capture as many patients as possible. However, this can lead to a number of difficulties:

> Different regulatory authorities may take a different view on the study, and different regulatory obligations may apply. This is particularly the case where the orphan disease involves children – we are aware of cases where ethics committees in the EU and the US (and even within the EU) have taken different views on whether a trial can be commenced or on the type of patients that can be included in the trial. There are also questions regarding the practical arrangements for global trials and the ability of investigators to comply with both the EU and the US rules. For example, the FDA requires Form 1572 to be signed for a clinical trial that will be included within a new drug application to ensure that the trial complies with FDA regulations. However, some EU member states take the view that investigators should not sign Form 1572, as any clinical trial conducted in the EU must be in accordance with EU law, and cannot be conducted under any foreign country legislation. It is possible to apply for a waiver from the FDA where the investigator knows they cannot commit to all of the requirements on Form 1572. Nevertheless, these types of divergences cause added complication and delays.

> The EMA and the FDA also take different views on the scientific aspects of clinical trials. For example, they may expect different endpoints for a clinical trial, such as which endpoint should be used as the primary endpoint for the trial in order to obtain a marketing authorization. See for example an analysis of the differences in EMA and FDA clinical development guidelines on medicines for the treatment of Alzheimer's disease. Similarly, the EU and US regulators have had different views on the appropriate comparator to use in the trial, given that it is rarely ethical to provide patients with a placebo when there is a potentially life-saving treatment on offer, and there may be differences in the standard of care in each region. That said, significant efforts have been made to harmonize regulators' approach to orphan development, and the data suggest that there is increasing concordance on data requirements and endpoints across the jurisdictions.

In such cases, companies should seek to explain their position to the EMA or the FDA and justify the approach they have taken from a scientific perspective, for example to explain the differences in the obligations being imposed, and why it is scientifically necessary to amend any such obligations and for the company to take a particular course of action. From our experience, the authorities usually understand the difficulties companies face. However, decisions on endpoints or comparators, and in what circumstances they should be changed, are more often a scientific rather than a legal or regulatory question. In certain cases, it may be possible to leverage the existing mechanisms for EMA-FDA regulatory discussions, as discussed above, to seek agreement between the authorities.

Data Required For Authorization

As noted, regulatory authorities do have some discretion when it comes to the level of evidence required to grant an orphan drug a marketing authorization. Also, there are schemes in place on both sides of the Atlantic to allow for quicker assessments, or approvals based on the iterative generation of data, starting with a narrow patient population and expanding this as more data become available. Such schemes, and the discretion of the regulatory authorities, can lead to greater divergence between the EMA and the FDA, such as at what stage a product can be approved and for what indication. For example:

> While the EMA and the FDA have introduced a process for providing parallel scientific advice on orphan products, there is no obligation on the agencies to come to the same view on the data required for marketing authorization. This causes difficulties for companies, for example, due to complications with analyzing data derived from studies with differing trial designs. There are also examples of cases where a product has been authorized based on one trial in the EU, but additional data is required in the US, or vice versa, leading to delay in the product being made available to patients.

Similarly, in cases where data sets are based on small numbers of patients, the regulators may take different views on what indication the product should be approved for. One authority may be more willing to approve a broader indication given the evidence in a narrow patient population and the potentially dramatic effects of the treatment, while the other may not be comfortable approving the product for patients who were not included in the clinical trial. A 2017 study found significant differences in the orphan populations with available therapies in each jurisdiction.

An increasing area of focus is the use of real-world evidence (RWE) in approvals. Although there is no clearly established regulatory framework in the EU for the use of RWE, the clear consensus is that it can produce supporting evidence for clinical decision making, although it is not a substitute for data from RCTs. In the US, Congress has enacted provisions directed at FDA policymaking on the use of RWE, and the agency has issued guidance on its development and potential use in supporting regulatory decision-making in certain scenarios as it develops broader policies and confidence in such data. Several companies have already utilized RWE in FDA submissions to bolster clinical data and accelerate approval. A divergence in EMA and FDA regulatory policy in this area could have a significant negative impact in the orphan area.

The EMA and the FDA also have different views on post-marketing obligations and the extent of pharmacovigilance requirements that may be required given the small numbers of patients included in clinical trials of orphan drugs. As such, post-marketing data collections may be required by one agency but not the other, or there may be different post-marketing obligations imposed. In all cases, once the data have been generated, both agencies will expect them to be submitted and reflected in the product label to the extent the information is useful for patients or impacts the risk-benefit profile.

Given these potential areas of divergence, companies should have strategies in place to manage their promotion of products with different indications in different jurisdictions. They should know how to engage with health care professionals and patients when questions are asked about why a certain product is not available in one or other country. As it is often smaller companies that market orphan products, there may also be a need to agree this strategy with commercial partners, including how additional trials will be paid for if they are only required in one country, or what marketing activities will be undertaken in each country. This can further complicate the commercialization of orphan products, which is already problematic given the difficult economic environment in many countries.

Conclusion

The legislation on orphan products in the EU and the US is similar, and there is certainly evidence of successful cooperation between the regulators in trying to ensure that the development of medicines for rare diseases is as streamlined as possible.

However, there are differences in relation to the terminology, requirements and assessment criteria. When companies are increasingly looking to globalize development, and products are more and more specialized, these differences can lead to delays in patients receiving life-saving drugs. They also lead to differences in terms of the authorized indications on each side of the Atlantic, and the timing of authorization. This is clearly unsatisfactory for both patients and regulatory authorities.

There is a need for key stakeholders to continue to harmonize their approach to orphan product development and regulation in the EU and the US. Orphan drug developers are also willing to work with the regulators to resolve differences in scientific opinion and help to streamline the process.

If differences remain, companies often prefer to follow the advice of the FDA, given the larger market opportunity in the US compared with the EU. This risk difficulties and delays with the authorization in the EU. If the EU wants to ensure faster access to orphan products, efforts to ensure harmonization with the US should be continued.