Orphan Drug Designations – Are the EMA and FDA Looking for the Same Information?

Whilst working on a recent European application for an orphan drug designation (ODD) for a rare neurological condition that was being made to the EMA, I noticed that there was a markedly lower number of ODD application approvals for that particular indication in the EU than in the US. I then looked at some other rare diseases, in case this was a peculiarity of this specific rare neurological condition but, no, for other indications there were also fewer registrations for ODDs in the EU than in the US. Now I was getting quite obsessed with this so decided to look in more depth at the total number of ODD applications approved in the US and EU.

Both the EU and US publish their orphan or rare disease designations in publicly available websites. The US gives a list of the generic name of the drug, the indication that has been granted the orphan drug designation; by clicking on the generic drug name you can find the drug’s trade name, the name of the sponsor and whether the drug has gained FDA marketing approval. Whilst on first look, the EU publishes a similar public listing (showing the name of the active substance and the name of the condition), if you click on the active substance then much more information is revealed, including:

- A summary description of the condition, including an explanation of how this condition is serious or life-threatening.
- The estimated prevalence of the condition in the EU. This summary does not give details of the references the applicant has made to justify this, but does summarise the conclusions made on the number of patients affected in the EU.
- Details of what treatments are available in the EU at the time of the application. A very useful source of information for anyone submitting an ODD application for a condition that already has achieved ODD designation.
- How is this medicine expected to work? This section contains a summary of the mechanism of action of the drug in the condition.
- The stage of development at the time of the submission of the application becomes public knowledge in this section. This can be whether the drug has been evaluated in experimental models or if clinical trials have been conducted or are ongoing.
- The name, address and contact details of the sponsor. Note the sponsor needs to be an EU resident so it may be an agent holding this on behalf of a non-EU entity.

Given this apparent greater transparency then you could perhaps assume that there would be more drugs for rare diseases granted orphan drug designation in Europe; after all, companies have access to the main pieces of prior knowledge that previous successful applicants have made.

But the EU ODD regulations are considerably ‘younger’ than their US counterparts, coming into force in 2000, compared to the US regulations that came into force in 1983. So could that be the reason? However, when you strip out the older designations and factor in the globalisation of the pharma industry in terms of drug development and the harmonisation efforts of the EU and FDA, are the numbers still lower? Let’s take a look.

As at the end of March 2015, there are 3387 ODD applications that have been approved by the FDA, since the regulations were introduced in 19831. However if this is limited just to ODD applications approved since 2000, the date the EU legislation came into force, this has a total of 2400 ODD applications approved.

In contrast, since the EU regulations were passed in 2000, to 31 March 2015, there are 1464 ODD applications recorded, including those applications withdrawn or with a negative opinion. If this is restricted to ODD applications approved, this number is 11682, a hefty 51% lower than the US. So why is this? On the face of it, the two sets of regulations are the same – or are they? Indeed, when you are dealing with both US and EU applications for the same ODD some important differences come to light that are crucial to ensuring you have a successful outcome in both jurisdictions.

What is an Orphan Drug Designation?
Firstly let’s recap briefly on what an orphan drug is. Well, firstly, it is not a rare drug but it is in fact a rare disease, and you are seeking to develop either a treatment, a diagnosis or a prevention for this. The drug could be an old drug or a new drug. Indeed there are a number of ‘old’ drugs that have no patent protection, that have then been found to be of use in these rare conditions that are then afforded marketing exclusivity – a key benefit of getting an orphan drug designation. In the US the terminology is orphan drugs; in the EU the terminology is rare disease designations.

What is a Rare Disease?
Now this is different depending on whether you are applying to the FDA or the EMA. In the US it is an absolute number and to be ‘rare’ then the condition must affect fewer than 200,000 people in the US3. In the EU it is an odds ratio of 5 in 10,0004. This can then accommodate the changing population and number of member states in the EU.

How do you Know if a Condition is ‘Rare’?
Evidence must be produced for applications to both jurisdictions that justify your claim that the condition is rare. The fact that someone else has obtained ODD approval for that same condition does set a precedent that will help your case, so a search of the ODD registers in the EU and US is always a good starting point. If there are no other approvals to act as a precedent, then you need to make the case from the literature or, if there are no published epidemiological studies,
What are the Differences Between the FDA and EMA?
One area where there is an important difference is that in the EU, the disease has to be not only rare, but also life-threatening or chronically debilitating. In the US, the condition needs to be rare and the reason why the treatment is needed must be explained.

Another reason for rejection of an ODD application by the EMA is that there is no data to support the use of your drug in the disease. It is not enough to have a hypothesis for the effect, data, preclinical or clinical needs to be provided. The EMA’s latest revision to the format and content of the application for designation for orphan medicinal product states:

'It should be noted that for the purpose of designation and to support the rationale for the development of the product in the proposed condition some preliminary preclinical or clinical data are generally required.'

The data to justify the use of the drug in the rare condition can be from preclinical or clinical sources. If it is preclinical data, then the EU will look for the applicant to substantiate the relevance of the animal model to the rare disease. This is another important point when drafting an application. The EMA will also critically evaluate the applicant’s data from the preclinical model to see that it supports the drug’s method of treatment, prevention or diagnosis being claimed.

This contrasts with the FDA, where the regulation remains that the sponsor must append a discussion on the rationale for the use of the medicinal product for the rare disease or condition, and whilst all relevant supporting information from non-clinical or clinical studies must be submitted, they are not necessarily required.

Another key difference between the EMA and FDA, is that the EMA require details of whether there are other methods for treatment available in the EU or not. So you need to search for all the possible approved treatments in your ODD indication and be aware there may be an old approved drug in some EU member states. This means searching each EU member state’s national approved drug register, and to help with this challenge, the EU have recently issued the following guidance. If there is already a drug approved for your orphan disease then it will be deemed to be ‘satisfactory’, no matter how effective it is and you will have to make the case that your drug will offer a significant benefit to those affected by the condition. Note this can be made on the basis of improved safety profile, or as improved efficacy or a major contribution to patient care (such as easier method of administration, oral vs IV). In all cases, the significant benefit argument needs to be justified by data. An illustration of this criterion serving as a basis for rejection of an ODD application by the EMA is for nabnilone as a treatment of amyotrophic lateral sclerosis (ALS). The negative opinion was based on the fact that the sponsor had not provided any data on the effect of nabnilone on ALS, and without data it was not possible to establish a potential significant benefit over current treatments.

The data to justify significant benefit can be from preclinical or clinical sources. Although companies may perform preclinical models with their drug, they do not always include the approved drug to provide comparative data. If there is already published data on the approved drug in your animal model then that could be used to support your position of significant benefit, however if the approved drug did not perform particularly well in the preclinical model then it is unlikely to have been published. As that data would be particularly useful, it is something to consider early in the development plan for the product.

It is important to note that the EMA publishes the reasons for negative opinions for the ODD applications, for those applications that proceed to a full vote by the Committee for Orphan Medicinal Products (COMP). It is possible for the applicant to withdraw an application if the trend of voting at the COMP is negative. If the applicant withdraws at this stage (prior to the formal vote) then it does not appear as public information. In contrast, the FDA publishes a limited amount of information only on those applications granted ODD.

What are the Advantages of Orphan Drug Designation?
So there seems to be a lot of work, and although there is an illusion of ‘harmonisation’, there still seems to be more work on the EU side. So what are the advantages for pursuing ODD approval in the EU and US?

Firstly there are important advantages which the ODD affords for both EU and FDA, and some important differences. In fact, I would be as bold as to say that if you get through the ODD approval process and engage with the EMA, through protocol assistance there is more opportunity for you to get approval in the EU than in the US. In both countries, marketing exclusivity is a big prize for an orphan drug, offering 10 years of marketing exclusivity in the EU and 7 years in the US; particularly attractive for an older drug off-patent. Both sides offer assistance with the protocols for pivotal studies, but whilst in the EU this is through protocol assistance, a special type of scientific advice specifically for orphan medicines that often involves the same people that reviewed the ODD application, in the US this is through the same process for all drugs. In
the FDA, once the ODD is approved for drug development aspects, then the drug company needs to engage with the division that will consider their IND and ultimately NDA; there is no link back to the Office of Orphan Products Development and no special orphan drug pathway to approval. In the EU there are two additional types of marketing approval that are available to companies with ODD. These are conditional approval and approval under exceptional circumstances. These additional approvals, whilst being by no means easy to obtain, at least offer an alternative route for companies working in rare diseases.

Finally the statistics: the EMA quote that of the 82 medicines approved in 2014, 17 were in rare diseases and special regulatory pathways were used for three of these medicines (two obtained conditional marketing authorisation and one obtained approval under exceptional circumstances).

In the US, the FDA granted approval to 44 new drugs in 2014, with 11% in rare diseases.

So in conclusion, obtaining orphan drug designation approval in the EU may prove to be more challenging than the US; however, once you have made it through the doorway it can offer additional paths and specific guidance on your journey to approval, which should make it all worthwhile.

References
1. http://www.accessdata.fda.gov/scripts/opdlisting/opd/OOPD_Results_2.cfm

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