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DEVELOPING NEWS

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Orphan Unknowns: What the MHRA Guidance Will Mean After Brexit

Developers of orphan drug products face some important changes with the approval process in the UK after Brexit. To help companies prepare, the MHRA published new guidance: "How the MHRA will manage orphan medicinal products from 1 January 2021 in Great Britain (GB)". While most of the criteria to qualify for orphan drug designation align with the EU, there are small but significant differences.

First, companies can only receive an orphan drug designation (ODD) when they apply for their marketing authorisation application, which means there will be no free protocol assistance or scientific advice. This sets MHRA apart from EMA, which offers discounted or free scientific advice as well as other avenues of support for orphan drug developers. The UK will continue to "offer incentives in the form of market exclusivity and full or partial refunds for marketing authorisation fees to encourage the development of medicines in rare diseases", although the details on how these compare to EU ODD incentives are yet to be released. Those wanting scientific advice from the UK agency can still receive it, however, unless they are designated in the UK as a small to mid-size enterprise, they will have to pay for that expertise.It is an interesting move by the MHRA but while there are certainly negative aspects to it, I believe there are also advantages. The following are some of the pros and cons that my colleagues and I have observed.

THE NEGATIVES

The MHRA is relying on companies going to the EMA with their clinical development plans. What that means for companies in terms of managing their endpoints and other criteria remains to be seen. For example, patient-reported outcomes (PROs) for your endpoints with rare diseases are notoriously difficult to get, especially with ultra-rare diseases where you may have only a handful of patients globally. That could pose a challenge for companies relying on some help from the agency on those PROs.

While it is assumed the MHRA will go along with EMA suggestions, there is a risk that UK assessors might not agree, in which case you may have to do additional work or look at something in your development programme differently. There may be difficulties navigating differences between MHRA and EMA opinions on protocol design or development plans. I don't think that's a big risk, but it is a consideration for sponsors, and one that may deter them from the UK market. And of course, there is a risk that if the process of bringing an orphan drug to the market in the UK is perceived as being too hard, lengthy or expensive, patients with rare diseases in the UK might not have access to a product that is available in the EU.

The orphan drug submission process must go through the centralised procedure in Europe, which is a massive undertaking, so the move by the MHRA could simply add to the regulatory burden. The UK market may be considered too small to be worth the effort.

THE POSITIVES

While EMA scientific advice is free, there is a huge time and expense commitment in preparing your

orphan drug package. It's certainly a useful exercise since it helps you focus your regulatory strategy, but it's complicated, time-consuming since approval through the centralised procedure at EMA requires agreement from all 27 member states. It may well be that going through the MHRA first – even if you do have to pay for scientific advice – is the more flexible route to take since you are working with one authority and one market, not 27.

There could be benefits to UK rare disease patients as well. If a company is developing products for several indications and one of those is an orphan indication, this can be used as a potential rapid route to revenue and to gain access to reduced fees for scientific advice. However, if the advice doesn't indicate rapid approval, it is not uncommon to see the company choosing to delay the orphan research and move forward on other areas first. The fact that they are continuing with development means they retain the orphan designation, which can discourage other companies from bringing forward products for the same disease since it is more difficult to get that fast approval for a subsequent orphan drug.

Subtle changes to the criteria for an orphan product in the new UK guideline – from "no satisfactory treatment can be authorised" to "no satisfactory treatment exists in GB" – requires that the orphan drug bring something new to the table and means companies can't apply for orphan status for established treatments which have never been through an authorisation process. And without that market exclusivity that comes with orphan designations, it means other products can come to market, making them more affordable for payers and patients.

THE WAY FORWARD

The MHRA claim to be prioritising access to new medicines – – and several other post-Brexit guidelines indicate a desire from the agency to become a competitive force in this area. There are still many unknowns about how Brexit will affect product approvals and, in particular, managing the orphan drug designation process and how this will impact access to medicine for patients with rare diseases in the UK. It will be a learning process for everyone – companies, consultancies, and the agencies – and there will inevitably be changes to deal with.

The pros and cons I have listed are just some of the possible outcomes. I would like to hear from other regulatory professionals and commercial decision makers about what you believe are the barriers and opportunities.