There are significant differences in the processes, policies and requirements for orphan drugs between the FDA and EMA.

**Definition of orphan status and incentives**

Incentives are defined on basis of population size, need and ability to achieve a return on investment. Table 1 highlights the key aspects of defining an orphan drug.

<table>
<thead>
<tr>
<th>FDA incentives</th>
<th>EMA incentives</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-month marketing exclusivity if the sponsor makes it available in the US within 3 years of approval.</td>
<td>Market exclusivity for 8 years of approval.</td>
</tr>
<tr>
<td>5-year market exclusivity if the sponsor makes it available in the EU within 3 years of approval.</td>
<td>Market exclusivity for 10 years of approval.</td>
</tr>
<tr>
<td>Assistance in drug development process.</td>
<td>Assistance in drug development process.</td>
</tr>
<tr>
<td>Availability of orphan drug products (also includes availability of placebo).</td>
<td>Availability of placebo.</td>
</tr>
<tr>
<td>Availability of orphan drug products.</td>
<td>Availability of orphan drug products.</td>
</tr>
</tbody>
</table>

Generally, the incentives offered are quite similar, although one key difference is that the tax credits applicable in the US are for up to 50% of the clinical investigation costs in the US, whereas the tax credit in the EU is limited to 30% of the total costs.

**Trends**

The study conducted a quantitative analysis on the publicly available data on orphan drug approvals released by the FDA and the EMA. By looking at the numbers of drugs approved, differences in the time for the approval decision and the reasons for rejections, the study was able to identify trends and differences in the organizations’ approval decisions.

**ORPHAN DRUG DESIGNATION: A COMPARISON OF POLICIES, PROCESSES AND RESULTS FROM THE US AND THE EU**

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**Methods**

We conducted a quantitative analysis on the publicly available data on orphan drug approvals released by the FDA and the EMA. By looking at the numbers of drugs approved, differences in the time for the approval decision, the indications (e.g. rare diseases, orphan drug designations and approvals across the limited numbers of patients to treat (and subsequent limited financial returns on financial investment). 1

In recent years the focus on orphan drugs has grown, with governments and regulatory agencies offering incentives to manufacturers of orphan drugs. 2

This study aimed to compare the policies and processes that influence orphan drug designation in the US and in the EU, and examined the approval data to explain any differences and/or trends in decision making.

**Results**

There are significant differences in the processes, policies and requirements for orphan drugs between the FDA and EMA.

**Objectives**

Pharmaceutical manufacturers can apply to the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for orphan drug status for new and existing products. Orphan drugs are defined as medicines or therapies designed for the diagnosis, prevention or treatment of a rare disease, i.e. a condition that affects fewer than 200,000 people in the US or fewer than 500,000 people in the EU.

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**Table 1: Orphan drug definition**

<table>
<thead>
<tr>
<th>FDA</th>
<th>EMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Drugs licensed for the safe and effective treatment of rare conditions.</td>
<td>• Drugs licensed for the safe and effective treatment of rare diseases.</td>
</tr>
<tr>
<td>• The rare disorder must affect fewer than 200,000 Americans in the US.</td>
<td>• The condition must affect fewer than 500,000 in the EU.</td>
</tr>
<tr>
<td>• Or it must be unlikely that marketing of the drug would generate sufficient revenue to justify the investment needed for its development.</td>
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</tr>
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In general, the definitions are very similar. There is a slight difference in the orphan definition, with the EU working out slightly higher than in the US (approximately 6 per 10,000 versus 5 per 10,000). The EMA states that no other satisfactory interventions should be available, or the new intervention must demonstrate a significant benefit, whereas the FDA does not state this as a requirement.

To encourage research and development for orphan drugs, both organizations offer a number of incentives for manufacturers as shown in Table 2. 1 This includes financial incentives, as well as help and support during the drug development process. This support, not given as comprehensively to standard drug products, may increase the likelihood of successful submission as manufacturers are able to discuss their proposed study protocols to check that they suit requirements for the organizations.

**Table 2: Incentives for manufacturers of orphan drugs**

**Case studies**

Some recent differences in decisions were identified. 3, 4 Three products that were assessed within the last 5 years were chosen as case studies; a summary of these is presented in Table 3. No case study could be identified for which the FDA rejected and the EMA approved a drug.

Manufacturers may prioritize FDA submission for many reasons. This may be due to the increased likelihood of acceptance, given the different data requirements, or it may be that companies wait to apply to the EMA until they are confident that they can demonstrate clinical effectiveness. The reasons may also be more general; some companies may focus on the US market initially for other reasons (e.g. size and perceived lack of barriers to market entry).

The likelihood of a drug gaining orphan drug status in either the US or the EU is dependent on a number of factors. Whilst the approaches taken by the organizations are broadly similar, some key differences mean that decision-making is not always aligned.

This study highlighted key differences, including:

- **Significant differences in eligibility criteria.** The EMA is more stringent than the FDA. Some orphan drugs that have been approved by the EMA are not considered as orphans by the FDA. For example, despite a positive risk benefit assessment at the 2010 Annual International Meeting, 16 “Or it must be unlikely that marketing of the drug would generate sufficient revenue to justify the investment needed for its development. An additional, “no satisfactory method of clinical investigation of the condition” (or similar such methods, the medicine must be approved for a condition that does not allow for trials). The EMA had already granted orphan drug status to this condition. The FDA accepted the same protocol for this condition. However, the EMA rejected it.

- **Orphan drug designation and approval if the product meets the requirements.** The FDA and EMA assess the efficacy and safety of a product, and can grant orphan designation and approval if the product meets the requirements. However, the EMA has rejected drug that had been approved by the FDA. For example, PSY76, an investigational drug for the treatment of advanced refractory metastatic colorectal cancer, was approved by the FDA in 2008 without evidence for all possible comparators (in line with their criteria stating that the new intervention must demonstrate a significant benefit over comparator options). However, the FDA encourages the collection of post-launch evidence and may grant approval stipulating the collection of evidence. This has happened on occasion, for example, when the EMA granted an orphan drug status for a product that was already approved on the basis of phase II trials in Europe.

These differences may be reflected in different numbers of approvals:

- The EMA approved 53 fewer orphan drugs than the FDA in 2005-2013. In the same period, the EMA approved 44 fewer orphan oncology drugs, a class that is about 40% of the total. The study supported a drug that was rejected on these grounds. The FDA approves drug for the treatment of a condition.” (called protocol advice). The EMA had already granted orphan drug status to this condition. The FDA accepted the same protocol for this condition. However, the EMA rejected it.

- **Differences in evidence requirements.** It appears that the FDA are more accepting of the clinical benefit of the proposed drug over comparator options (in line with their criteria stating that the new intervention must demonstrate a significant benefit over comparator options). However, the FDA encourages the collection of post-launch evidence and may grant approval stipulating the collection of evidence. This has happened on occasion, for example, when the EMA granted an orphan drug status for a product that was already approved on the basis of phase II trials in Europe.

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Overtime, the FDA’s rate of approval is converging with that of the FDA. Whilst the total number of decisions has increased, the reasons for rejections have remained. The analysis was limited due to the available evidence (for example, data on rejections across the time horizon could not be found). Additionally, there are likely to be numerous confounding factors affecting submissions that may affect decision making.