Orphan drug designation in the EU and the US – a critical review

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To encourage the research and development of orphan drugs, regulatory procedures and financial incentives have been implemented worldwide. In the EU and US, these programs are maintained by EMA/Committee for Orphan Medicinal Products (COMP) and FDA/Office for Orphan Product Development (OOPD), respectively.

Aim

To compare and identify differences between the orphan drug designations in practice in the EU and the US. The major theoretical differences between EU and US are described in Table 1.

Methods

Publicly available information on orphan designations and approvals released by the FDA and EMA were analysed:

- Period 2000-2016;
- Reasons for a negative designation opinion (opinion summaries and meeting minutes from COMP);
- Opposing designation opinions by COMP and OOPD .

Results

Database searches showed that that approximately 65% of orphan drug applications are granted approval by the US OOPD/FDA and EU COMP/EMA in 2000-2016 (Table 2, Figures 1 and 2, 2394 out of 3449 and 1398 out 2092 applications, respectively). Reasons for negative opinion are depicted in Figure 3.

The differences in application criteria may account for the higher number of applications submitted to the OOPD compared to the COMP. For instance, EMA orphan designation requires lack of alternative treatments and demonstration of significant benefit, whereas the FDA considers these to be requirements for orphan market exclusivity rather than for destination.

We identified cases in which the active substance had been granted designation by OOPD, but not by COMP. Analysis of COMP opinion summaries and FDA guidance showed:

- Both agencies stress the importance of the proper justification of prevalence;
- COMP puts more emphasis on the inclusion of relevant preclinical data;
- COMP, not OOPD, performs a designation maintenance check during the review of the marketing authorisation application; if significant benefit compared to other products is not proven, COMP may recommended that the orphan designation should not be endorsed (approval without the orphan incentives)

Table 1: Major differences between the EU and US

	EU	US
Designation Criteria	• Prevalence • Life-threatening or chronically debilitating condition, or • Return of investment **AND** • No satisfactory treatment, or • Significant benefit	• Prevalence, or • Return of investment
Pre-submission meeting	Yes!	No
Review timeline	• Fixed timeline • Deadline • Up to 120 days	Typically 90 days
Review	Plenary discussion COMP	Three level review OOPD
Appeal	Yes	No
Public information	• EC/EMA website • Rare disease designation database	Orphan drug designation database

Table 2: Orphan drug approvals EU & US

EMA 2000-2018		FDA	1983-1999	2000-2016
Positive opinion	1398	Desig-nated	428	2394
Negative opinion	21			
Withdrawn	311			
Expired	28			

Figure 1: Orphan applications and designations EMA

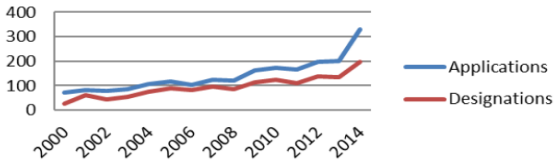


Figure 2: Orphan applications and designations FDA

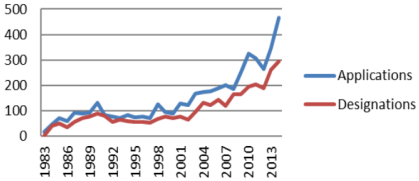
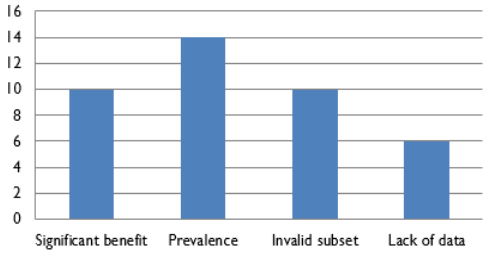


Figure 3: Reasons for negative opinions



Conclusion

Our analyses show that more criteria need to be fulfilled in the EU compared to the US to obtain orphan designation and marketing approval. This may influence the choice of regulatory strategy for orphan drug designation, and could explain the differences in the number of applications submitted to OOPD and COMP.