

## **EU Pediatrics Rules are Top Regulatory Headache for Drug Companies; Variations and Fees Close Behind**

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The pediatric medicines legislation is the area in the EU drug regulatory system that companies are most concerned about and believe are of "high-priority" for improvement.

The Variations Regulation, the new pharmacovigilance legislation and the costs and fees needed to fund the EU regulatory system are also high on the list, according to a survey in which 39 companies graded 91 regulatory areas on the degree of improvement needed.

The survey was conducted by members of the Escher Project\*, a private-public partnership that operates under the umbrella of Dutch "independent research enabler" Top Institute Pharma and which partners with authorities, academic institutions, companies and NGOs. It is part of a much larger, data-driven initiative by Escher Project members who are working on generating evidence on the underlying problems with the regulatory system for marketing authorization and determining how to fix them without having to change legislation.

The members expect to complete the

marketing authorization system initiative later this year and then use their findings to inform the agenda for policymaking at the European and national level. In the meantime, they are urging more drug companies and others involved in the industry to provide them with data and participate in their surveys, interviews and discussions.

### **'Valuable data' and a 'powerful report'**

"We are going to have an awful lot of data and evidence to present before the new [European] Commission and new [European] Parliament," said David Jefferys, who is involved in overseeing projects conducted by the Escher Project. Dr. Jefferys, who is also senior vice president of Eisai Medical Research, UK, said: "The report we write is going to be very powerful." The report is scheduled to be prepared and disseminated before November.

The latest survey received almost 1,000 comments, said Jean Philippe de Jong, who is leading the marketing authorization system initiative. The 39 respondents were member companies of R&D drug industry federation EFPIA and self-medication trade

group AESGP. "The survey resulted in a vast amount of valuable data," said Dr. de Jong, who is also a co-founder of Exon Consultancy. "Over 60 detailed examples of problems [companies encountered] were provided."

Particular issues cropped up more frequently than others in the survey. The below table shows the top 12 areas of concern. These related to various aspects of the Paediatric Regulation and pediatric investigation plans (PIPs). Companies also raised concerns over a lack of harmonization between the EU member states regarding product information, the decentralized procedure (DCP) and over-the-counter medicines.

Several aspects of the new pharmacovigilance legislation were also flagged up as problematic as were the timelines and fees associated with variations.

Other regulatory areas in the top 12 list included risk management plans and the mutual recognition procedure (MRP). Companies also expressed worries over the European Medicine Agency's conditional marketing authorization procedure, accelerated assessments and new regulatory pathways such as adaptive licensing. They also raised concerns over confidentiality and transparency measures by authorities and the release of trial data and data exclusivity.

### Survey results on areas in EU regulatory system for marketing authorization most in need of improvement

| Topic  | Mean Score <sup>#</sup> |
|--|-------------------------|
| Pediatric medicines  | 2.44                    |
| Variations (eg type IA/IB/II/unforeseen (Article 5) variations)  | 2.29                    |
| Other areas in the pharmacovigilance phase   | 2.29                    |
| Costs/funding of the system (including fees)   | 2.20                    |
| Article 46 (Paediatric Regulation) – pediatric study   | 2.19                    |
| Transparency and accountability (eg confidentiality, transparency measures, release of trial data, data exclusivity) | 2.17                    |
| Harmonization (eg between EU member states, between EU and other regions)  | 2.14                    |
| New regulatory pathways (eg adaptive licensing)  | 2.14                    |
| Conditional marketing authorization  | 2.09                    |
| Accelerated assessment   | 2.08                    |
| Risk management plans  | 1.97                    |
| Mutual recognition procedure   | 1.97                    |

#Ranked according to mean score. "Mean score" is mean of respondents that scored the area. A score of 0 indicates no need for improvement and a score of 3 indicates a high need for improvement.

*Source: Jean Philippe de Jong slide presentation at 26<sup>th</sup> annual DIA EuroMeeting on 26 March.*

### Four high-priority areas

Dr de Jong's team recently began conducting in-depth studies on four high-priority areas:

- the timing relating to when a company must submit a PIP;
- the use of the conditional marketing authorization pathway;
- the impact of the pharmacovigilance legislation; and
- the effects of objections that are raised by member states during DCPs/MRPs.

Data collection for all four studies is scheduled for completion by the end of April.

### The problems with PIPs

In the PIPs study, the investigators are evaluating whether submitting a PIP early on – as is required by law – is of any benefit.

The need to submit the PIP early is "something that a lot of companies are not happy with," Dr de Jong noted. Companies feel the deadlines are too early for three reasons: the information required is often unknown, leading to downstream modifications; failure of compounds lead to redundant PIPs; and activities for PIPs in the

EU cannot be aligned with equivalent submissions in the US.

More specifically, the study investigators are evaluating "how the timing of PIP submission relates to the availability and quality of information about the use of medicines in children." Among other things, they are analyzing a sample of PIPs (and PIP waivers) that were agreed by the EMA's pediatric committee, the PDCO, in 2008, 2009 and 2010. They are also looking at data from a previous EFPIA survey on PIPs.

### Understanding why conditional authorization is not working

Regarding conditional authorizations, both regulators and companies are concerned that this pathway is not being used as it should be. "That's a shame because I think the conditional approval legislation is a very nice piece of legislation," Dr. de Jong commented. The Escher Project members are seeking to understand the motives for designing the conditional pathway and initial expectations on how it was supposed to function in regulatory practice. They plan to create "regulatory profiles" of drugs that are likely to be approved via pathway. They will

study how interactions between marketing authorization holders and regulators are organized during the marketing authorization process (from scientific advice to the fulfilment of specific obligations). Finally, they hope to learn how they can evaluate new regulatory pathways, "especially in light of the anticipated move towards more adaptive approaches," Dr. de Jong said, adding that "we don't want to make the same mistakes...here."

The conditional authorization study investigators are focusing on oncology drugs because the pathway is "mostly used for these products." They are analyzing data from such things as European public assessment reports (EPARs) and summaries of product characteristics for drugs that have received conditional authorizations. They are also interviewing companies, regulators and policy makers on the authorization process for products approved under the conditional pathway.

So far, they have a database of 61 oncology products that have been approved by the EMA and/or US Food and Drug Administration since 2006, of which 11 received conditional authorization. They have also conducted nine interviews and plan to conduct more.

### **Questions on the added value of pharmacovigilance**

The pharmacovigilance legislation study is assessing the cost and impact of the new law. For example, the study investigators are seeking to understand to what extent the different pharmacovigilance instruments (for example, clinical studies/post-authorization safety studies (PASS) and spontaneous reports) contribute to identifying new safety information. They are looking for insight into what might be the added value of PASSs and clinical studies as compared to routine pharmacovigilance only. They will also assess the costs of complying with the legislation compared with the projections that were made by the EMA in 2008. The study is analyzing data from EPARs and post-marketing safety variations. The investigators are also conducting a survey of EFPIA and AESGP companies on the costs of complying with the pharmacovigilance requirements; the survey's deadline is mid-April.

### **Objections during DCPs and MRPs**

Finally, the Escher Project investigators are seeking to gauge how industry is affected by member states using their prerogative to raise objections during DCPs and MRPs. Objections can be raised on the grounds of potential serious risk to public health. However, the frequency, content and effects of objections are unknown.

The study investigators are identifying how often objections are raised, the nature of

these objections and whether they really are public health risks, and what consequences they have – for example, application withdrawals or refusals. They are making a systematic inventory of the reasons for objections raised in order to find commonalities. So far, they have looked at DCPs and MRPs that were finalized between June 2006 and December 2012 (6,511 and 3,919, respectively). They have found that nearly 4% (373) of these DCP/MRP procedures in total were referred to the Co-ordination group for Mutual Recognition and Decentralised Procedures (human), and around 1% (105) was sent to the EMA's CHMP scientific committee for arbitration. However, Dr. de Jong pointed out that the figures on objections are, in fact, much higher than that reflected in the analysis, which has not caught the many companies that, on receiving an objection, withdraw their application.

Commenting on the value of the work by his Escher Project team, Dr. de Jong said that "measuring performance of the regulatory system can be an incentive for reform and can support an evidence-based discussion on how to improve the system." The current EU laws governing the marketing authorization

procedure "provides considerable leeway for improving the system," he said.

David Jefferys and Jean Philippe de Jong were both speaking at the 26<sup>th</sup> annual DIA EuroMeeting in Vienna on 26 March.

*\* The Escher Project was launched in 2008 to identify, evaluate and remove regulatory bottlenecks hampering the efficiency in pharmaceutical innovation and stimulate factors helping innovation. It is a public-private partnership between Utrecht University, University Medical Centre Utrecht, University Medical Centre Groningen, Erasmus University Rotterdam, GlaxoSmithKline, Amgen, the Royal Dutch Association of Pharmacists and MSD, and it operates under the umbrella of Top Institute Pharma. According to the organization's website, the Escher Project brings together expertise from a wide array of disciplines, institutions and countries. The initiative that is investigating how to improve the EU system for marketing authorization is one of a number of projects that the Escher Project members are conducting.*

*References for this article are available upon request.*

