EVENT REPORT

THE REVISION OF THE EU LEGAL FRAMEWORK FOR ORPHAN DRUGS AND ITS IMPACT ON GERMANY

5 SEPTEMBER 2022
VIRTUAL WEBINAR

Presented by:

EUCOPE
European Confederation of Pharmaceutical Entrepreneurs AISBL

BPI Bundesverband der Pharmazeutischen Industrie e.V.

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Introduction

On September 5, 2022, the European Confederation of Pharmaceutical Entrepreneurs (EUCOPE) and Bundesverband der Pharmazeutischen Industrie (BPI) organised an online event **on the revision of the EU regulatory framework for orphan drugs and its impact on Germany**. The upcoming revision was discussed together with patient representatives, policy makers, regulators, physicians and representatives of the industry. More than 200 attendees participated at the event.

The discussion focused on the opportunities and risks of the expected changes to the Orphan Medicinal Product Regulation (**Regulation 141/2000**) and the interplay of this reform with the discussed **draft bill on the "Financial Stabilisation of the Statutory Health Insurance System** in Germany.

The political landscape in the EU and Germany, *Dr Alexander Natz, EUCOPE*

I. The development at European Union level

In his introduction, *Dr Alexander Natz,* Secretary General at EUCOPE, presented the possible changes to the current EU legal framework. The European Commission is expected to present a proposal for revision of the **Regulation 141/2000**, governing the designation and the incentive of medicines for rare diseases in Europe. Among the measures that the Commission is considering, he highlighted the condition to market orphan drugs in all member states in order to receive the highest level of incentives; the possible introduction of the concept of high unmet medical need in the legislation and of a modular system for incentives.

II. The development at national level in Germany

Dr Natz also touched upon national developments in the field of orphan drugs. The German Ministry of Health draft bill on the "Financial Stabilisation of the Statutory Health Insurance System" includes measures that will greatly impact the pharmaceutical industry and availability of orphan medicines to patients.

Currently, the benefit of orphan drugs with a volume sale below EUR 50 million is assumed by law, i.e. they do not have to undergo a full cost effectiveness assessment. This EUR 50 million threshold would be lowered to EUR 20 million. Once the annual sales within the statutory health insurance system exceed this threshold, a complete assessment procedure has to be conducted. This would have a severe impact on all future launches of orphan drugs in Germany.

III. A preliminary assessment of the possible impact

Dr Natz noted that such reforms would pose major challenges, especially for small and medium-sized companies. A modification of the European incentive system as planned by the Commission would impair the competitiveness of the European industry.

- Contrary to the goal of the current legislation of promoting orphan drugs in the EU, the reform risks decreasing EU's attractiveness as a market for orphan drugs in comparison to the US.
- A restrictive definition of high unmet medical needs is dangerous and counterproductive. The assessment in the EU member states is heterogeneous; in Germany, the "Nikolaus judgment" of the Federal Constitutional Court should be observed.
- A comprehensive market launch in all EU member states is difficult, especially for the often very small (single-product) companies. In addition, there is not an HTA procedure in all countries. The political goal of broad access to innovations can also be achieved working with the EU legal framework for on cross-border health care. There are clear limitations in introducing a medicine for a total of 30 EU patients in 27 member countries.

- The current German legislation takes the assessment of the product's benefit during the regulatory process with the EMA into account. It would definitely be detrimental to the availability of these products and patient access if changes to the current law would be introduced that ignore the specific regulatory processes for OMPs at EU level.

Moderated Panel

Opening Keynote

Prof. Dr. Andrew Ullmann, Member of the German Bundestag opened the panel with a keynote speech.

He emphasised the importance of a well-adjusted incentive system in the field of orphan drugs as there is still no approved therapy for the vast majority (95%) of rare diseases. According to Prof Dr. Ullman, an update of the current system is needed. The question should be how to incentivise research. Case studies could also be sufficient for extremely rare diseases (e.g. 30 patients in the EU) to grant provisional approval. The classic randomised clinical trials are not possible in this situation.

Regarding the draft bill on the "Financial Stabilisation of the Statutory Health Insurance System, Mr Ullmann mentioned that the provisions outlined in the draft are not set in stone; the parliamentary procedure is just beginning. According to him, structural changes are needed to ensure sustainability.

Dr. Miriam Schlangen
Dr. Miriam Schlangen, head of the National Action League for People with Rare Diseases (NAMSE) and Cystic Fibrosis Association (Mukoviszidose e.V.), pointed out the importance of well-managed patient registries. Using cystic fibrosis as an example, she explained the difficulties associated with defining unmet medical need, which is currently being discussed as a key feature for incentives as part of the revision of the EU orphan drug legislation. From the point of view of cystic fibrosis, for instance, the EU regulation for orphan drugs is "a blessing". There is now an effective drug that does not cure certain patients but has a very good (mitigating) effect. Because the effect only occurs in a group of patients, the problem of different additional benefits for the same active substance arises here (the G-BA assesses the additional benefit separately according to individual patient groups). There is already a German register for cystic fibrosis, this is the kind of basis we need to conduct further research.

The example of cystic fibrosis shows how difficult it is to define a high medical need, given the heterogeneity of patients' response to treatments. Even for patients that do have therapeutic options like in the case of cystic fibrosis, they would have to deal with therapy for about five hours a day. How can this suffering be evaluated in comparison with a disease for which there is no therapy at all?

Mr. Martin Lack
Mr. Martin Lack, Head of Pharmaceuticals Department, National Association of Statutory Health Insurance Physicians (Kassenärztliche Bundesvereinigung), emphasised the importance of robust clinical trials, even for rare diseases, based on the experience of the early benefit assessment. The experience of the G-BA shows that good evidence in the form of randomized controlled trials is often available for orphan drugs at the time of market entry. If this is lacking, it is often not possible to generate it later, or only at great expense.

He explained that in retrospect, the special status of orphan drugs in the European Regulation 141/2000 is a great success as a third of the new launches are orphan drugs. However, the high prices are a problem for the finite health systems finances, hence new measures are needed. It's about keeping the balance. Research with registry data is difficult. The patient representation in the G-BA attaches great importance to comparative data (i.e.: direct comparison within a study; not: comparison with data from other patients that are collected in registries). He does not consider case reports from individual patients to be sufficient.

Mr. Matthias Heck,
Mr. Matthias Heck, Senior Director International TA Policy Strategy/ Government Affairs & Policy (EU/Germany), Alexion Pharmaceuticals pointed out that the planned new legal framework has so far not addressed economic feasibility. He explained that orphan drugs must be considered in an holistic manner. The political measures at European and German level, the finances of the statutory health

insurance and the environment (care, research, industry) are particularly relevant here. In order to promote mutual understanding, industry should be involved. Mr Heck added:

- Halving the rates (in the EU: five instead of ten years of market exclusivity; in the G-BA: 20 instead of 50 million turnover threshold) is counterproductive.
- Medicine availability in all EU member states is a key common goal; an obligation for the manufacturer, however, is inappropriate, because the successful outcome of a P&R process is not solely in the hands of marketing authorisation holders.
- An AMNOG reform is justified. However, a quick revision as part of an austerity law and without the involvement of all stakeholders is counterproductive.

Q&A

A lively Q&A discussion followed the panel intervention. Frauke Naumann-Winter, representative of the BfArm (Federal Institute for Drugs and Medical Devices) at EMA for Orphan Drugs mentioned that 60% of the approvals for orphan drugs were based on randomised clinical trials (RCTs). Once the active working principle of a new active substance is understood, new applications can be researched with less effort. The "TOX studies" (examination of the extent to which an active substance is toxic to the human organism) are then already available.

She continued to explain that conditional approvals (e.g. with the requirement to carry out further studies) render the benefit assessment very challenging. Therefore, she believes, approval and (research) funding should be "decoupled". For example, funding is urgently needed to develop therapies for children with cancer because there are very few patients in those areas. In addition, registers are important. Especially for very rare diseases, concepts for studies (endpoints) could only be developed if sufficient data had been collected beforehand. The "HTA Bodies" (in Germany: G-BA and IQWiG) should participate in registries so that future studies would be possible. In addition, she mentioned that the concept of “unmet medical need” is difficult to operationalise. For every (theoretically avoidable) death there is an unmet need. But there are still many diseases that are not understood. She mentioned that there is a much greater need for research there.

Conclusion

Finally, Matthias Wilken (BPI) summarised the event. In the case of medicinal products for rare diseases, two political strands are currently running in parallel: the EU is revising the regulatory framework (advantages of approval and market exclusivity) and the Bundestag is discussing an AMNOG reform.

The German AMNOG treats orphan drugs according to EU approval criteria. The two strands of regulation are indirectly related. Without careful consideration of the impact and implications of the discussed provisions we risk that the combined effect of these two reforms produce a double damage.

To further advance a European strategy on rare diseases as well as the discussions on areas of unmet needs, an open exchange with all stakeholders should continue to take place in order to avoid hampering the achievements of the current system.