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RARE DISEASES IN THE SLOVAK REPUBLIC
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ORPHAN DRUGS IN EU

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Medical and scientific knowledge about rare diseases is minimal or lacking, thus making research difficulties for pharmaceutical industry. Orphan drugs in EU are under supervision of European Commission, European medical agency (EMA) and Committee for orphan medicinal products (COMP).
The presentation provides a brief review of all supportive incentives in the field of orphan medicinal products as: the European orphan medicinal product (OMP) regulation, Guideline on Clinical Trials in Small Populations and Commission Regulation (EC) No 2049/2005 / support of small and medium enterprises (SMEs). It also introduces the concept of Clinical added value of orphan medicinal products, as one of the key instruments to increase the availability of orphan medicinal products in the member states. Separately it stresses the necessity of Health technology assessment implementation in whole process of orphan medicinal product development as well as the implementation of the Europlan indicators into the Slovak National plan

Keywords: *orphan drugs – policy in the field of orphan drugs – European orphan medicinal product (OMP) regulation*

Medical and scientific knowledge about rare diseases is minimal or lacking, thus posing research difficulties for pharmaceutical industry. Orphan drugs in EU are under the supervision of European Commission, European Medical Agency (EMA) and Committee for Orphan Medicinal Products (COMP).
The European orphan medicinal product regulation EC/141/2000 came into force in April 2000. Its main aim is to support equal treatment for patients with rare disease.

In June 2000 first applications were validated and in July of the same year first marketing authorization was approved (bosentan, Tracleer).
European support of research and drug development for rare diseases is provided in two steps. The first one, so called designation, could be given free of charge in every stage of the OMP development. However, the investigated OMP has to fulfil following criteria:

1. Seriousness of the condition

The investigated drug must be intended for diagnosis, prevention or treatment of a life-threatening or chronic debilitating condition.

2. Low prevalence/irretrievable investment

The prevalence of the condition, for which the OMP is intended, must be less than 5 in 10,000 or the investigated OMP must be unlikely to generate sufficient return to justify the investment.
In some situations, the condition is defined as a subset of another frequent condition. To accept the subset, it is needed to prove that the subset is medically recognizable and the investigated OMP will be effective only in this subset and not in the condition per se.

3. Medical need

No other treatment is authorised in EU for this condition or if there is one, the designated OMP must provide a significant benefit over the existing method. The significant benefit is given on the basis of/upon clinically relevant advantage or major contribution to patient care EC/847/2000.
The application for designation should follow European Commission guideline ENTR/6283/00 on format and content for OMP application. Together with further required supportive documentation it must be provided in three copies and also submitted electronically. The submission is free of charge.
The designation is possible only prior to marketing authorisation. It can't be given retrospectively!
Every application is validated by EMA and afterwards 2 coordinators are appointed (1 EMA, 1COMP). COMP adopts opinion by consensus or 2/3 majority within 90 days. For this reason presence of delegates from every member state is necessary! In case the provided information is disputable, the sponsor is asked to clarify it in a written or oral form. This, of course, prolongs the duration of the final opinion. The final information about the designation is published in Public summary of opinion on orphan product (EPHAR) at the EMA website.
After receiving designation, the sponsor is obligated to send annual update on development status and do so for the whole duration of the OMP status. This might include summary of development, administrative as well as regulatory update.
The orphan designation provides the holder several benefits, of which 10 years of market exclusivity (+ 2 if the drug has paediatric indication) is of the highest importance (others include: financial support for research, protocol assistance – development as well as regulatory assistance, fee reduction).
Another important relief is the centralised procedure of marketing authorisation, which could be marked as the second step of OMP development support. This is provided by the CHMP. However, COMP is also involved, namely in the reassessment of the orphan status. Special attention is paid to the similarity assessment (with

previously authorised OMP). The final result is published in the European assessment report (EPAR) on EMA website http://www.ema.europa.eu/ema/index.jsp?curl=/pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124.

Over 12 years of its existence, 1118 designations were approved, based mainly on the prevalence criterion. In total 80 orphan medicinal products were authorised, which means about 72% success rate. Approximately 60 different rare conditions are treatable nowadays.

This is in sharp contrast with 8 medicines intended to treat rare and serious conditions before this regulation.

Guideline on Clinical Trials in Small Populations

Another European incentive fostering the development of drugs for rare diseases is the Guideline on Clinical Trials in Small Populations, which came into effect at February 1 2007. It was prepared in cooperation of Committee for Medicinal Products for Human Use (CHMP), COMP, and Scientific Advice Working Party (SAWP). It might solve the problems associated with clinical trials in limited numbers of patients available to study, as is the case of several rare diseases. In this document, strategies for the approach to trials under such circumstances are briefly outlined. It emphasizes the existence of approaches, which increase the efficiency of clinical trials, by taking into account weighting of statistical efficiency against clinical relevance and thus increasing the interpretability of the results, which is most important at the end. On the other hand, deviation from standards is uncommon and should only be considered when completely unavoidable and would need to be justified. Regulatory assessment may accept different approaches only in situations if they ensure that the patients' interests are protected. In conditions where very few patients are available, non-clinical pharmacology may be of importance. Surrogate endpoints may be acceptable but need to be fully justified. Their relation to clinical efficacy must be clear so that the balance of risks and benefits can be evaluated. Control and comparator groups are very important. Their absence compromises the reliability of studies.

Commission Regulation (EC) No 2049/2005 / support of small and medium enterprises (SMEs)

In the field of rare diseases, incentives other than financial ones frequently play the main role. It is not rare that SMEs are highly motivated to study treatments for rare diseases. To support these incentives the EMA has implemented Commission Regulation (EC) No 2049/2005. The Regulation describes implementation of provisions concerning SMEs in the European Union pharmaceutical legislation. It was adopted on December 15, 2005 and aims to promote innovation and development of new medicines by SMEs.

CAVOMP to solve different access to OMP

The facts above support the indubitable success in proactive approach to rare diseases and raised awareness in this topic. On the other hand, only 1% of rare diseases are treatable and the patients with rare diseases face several problems, major of which is the still unmet medical need. Even treatable rare diseases are stricken. It is a problem to follow the transparency directive. The timing of reimbursement processes is extremely variable. Authorized OMPs are not equally available in all member states (Pricing & Reimbursement of the EU High Level Pharmaceutical Forum). There are

limitations in patients' access. This point is a crucial one, since the health benefits of an orphan drug can only be realised if patients get access to them.
To address this issue, several policy documents have recently called for an increased cooperation between EU-level authorities and Member States in order to improve the access to Orphan Medicinal Products for people living with rare diseases:
- The EU Regulation on Orphan Medicinal Products EC/141/2000;
- Final Conclusions and Recommendations of the EU High Level Pharmaceutical Forum
- The Commission Communication on "Rare Diseases: Europe's Challenges"
- The Council Recommendation on a European Action in the Field of Rare Diseases, adopted by the Health Council on 9 June 2009.
In this framework, a study by Ernst and Young was conducted to discover the feasibility of creating a mechanism for exchange of knowledge on the Clinical Added Value for Orphan Medicinal products (CAVOMP). CAVOMP should concentrate at the process of knowledge exchange between Member States (MS) as well as between the national level (MS) and EU level (e.g. European authorities and other EU bodies) without creating new hurdles, respecting both the legislative framework and the current and emerging roles and responsibilities of all actors involved (Figure 1). It means formation of permanent cooperation mechanism for health technology assessment (HTA) as defined in the EU "Cross-Border Healthcare Directive" as well as expansion of collaboration between the EMA and the European net of HTA (EUnetHTA). This has already led to specific cooperation on the improvement of EPARs. CAVOMP supports the early dialogue and scientific advice, including multi-stakeholder pilots; post-launch collaborative data collection; exchange of and comments on methodological guidelines; and potential collaboration in areas such as the assessment of significant benefit, added clinical benefit, and clinical superiority. It is a voluntary process, and should be conducted on a case-by-case basis. Each approach will be adapted to a specific disease and potential orphan medicinal product in question.

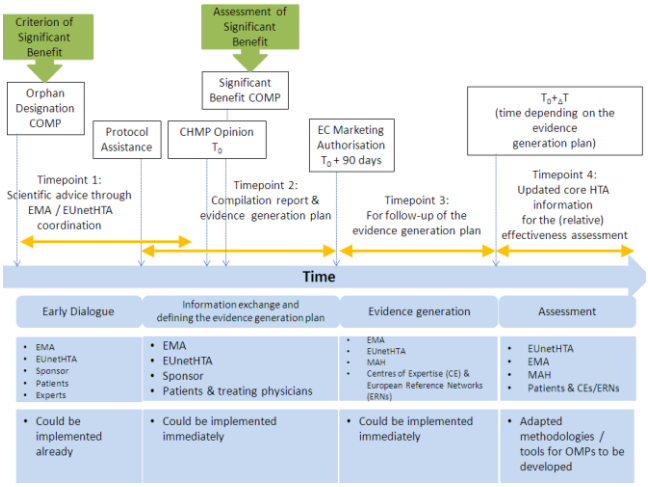

Figure 1 CAVOMP

In addition to CAVOMP, other on-going working groups in this area exist, such as the one on a Mechanism for Coordinated Access to Orphan Drugs (MoCA) within the Process on Corporate Responsibility in the field of Pharmaceuticals – Platform on Access to Medicines in Europe.

CONCLUSION

There is no doubt about the European support of orphan drug development in last 12 years. The interest is now in long term orphan drug access. On one hand it is a question of the extent in harmonizing reimbursement policies among the 27 EU countries; on the other hand, governments, the EMA, industry, payers and patients, need more collaboration in order to align everyone's interests. Involvement of all stakeholders in different parts of OMP development as introduced in the CAVOMP may guarantee the success.

REFERENCES

Regulation (EC) No 141/2000 of the European parliament and of the council. Off J Eur Commun, 2000, 43, L18:1-5.

Regulation (EC) No 847/2000, Off J Eur Commun, 43, 2000, L103, p. 5-8.
European Commission guideline ENTR/6283/00.
(http://www.ema.europa.eu/ema/index.jsp?curl=/pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124). Accessed February 20 2013.

Guideline on Clinical Trials in Small Populations.
(http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003615.pdf). Accessed February 20 2013.

Commission Regulation (EC) No 2049/2005.
(http://ec.europa.eu/health/files/eudralex/vol-/reg_2005_2049/reg_2005_2049_en.pdf)
Accessed February 20 2013.

Rare Diseases: Europe's Challenges.
(http://ec.europa.eu/health/ph_threats/non_com/docs/rare_com_en.pdf). Accessed February 20 2013.

The Council Recommendation on a European Action in the Field of Rare Diseases, adopted by the Health Council on 9 June 2009. (http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2009:151:0007:0010:EN:PDF)
Accessed February 20 2013.

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LIEKY NA ZRIEDKAVÉ CHOROBY V EÚ

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Výskum v oblasti terapeutických možností zriedkavých chorôb je náročný. Najväčšou prekážkou sú chýbajúce informácie o patogenéze tejto skupiny ochorení. Situáciu výrazne komplikuje nízka prevalencia. Príspevok prináša prehľad aktivít zameraných na podporu vývoja liekov na zriedkavé choroby na európskej úrovni. Tiež sa venuje vysoko aktuálnej problematike riešeniu problému rozdielnej dostupnosti liekov na zriedkavé choroby v jednotlivých členských štátov. Osobitne zdôrazňuje význam HTA pre sprístupnenie liekov na zriedkavé choroby v členských štátoch. Riešenie tohto problému je potrebné implementovať HTA do celého procesu podpory vývoja liekov na zriedkavé choroby od designácie až po registráciu.

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