The role of the Orphan Drugs initiative

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The Orphan Regulation (EC) No 141/2000 has been successful in stimulating R&D investment and new medicinal products tailored for rare diseases, offering several interesting incentives for companies. These incentives include free access to scientific advice during non clinical and clinical drug development programs (‘protocol assistance’); reduction in fees payable to EMA for review of the marketing authorisation and subsequent license maintenance fees, market protection in terms of market exclusivity in addition to a range of European and national incentives. This has favoured an increase in the number of applications submitted and, subsequently, granted.

So far over 850 applications for orphan designation have been submitted and, to date, these have translated into more than 50 products being approved in Europe for the treatment of rare conditions. Today orphan drugs constitute a solid reality. However, barriers to the development of orphan medicinal products still exist because of the small number of patients affected, the wide geographical widespread, the non-rewarding markets and the insufficient incentives. Additional difficulties arise from the consideration that orphan diseases are heterogeneous, with low prevalence and with often poor or relatively short survival rate. To this regard, the scientific advice/protocol assistance procedure represents a valuable tool to guide the drug development process in rare diseases. In particular, there are issues which are specific for orphan drugs and can be scope for the advice. It is a free of charge procedure and can be requested at any stage of the development by a sponsor who can be either a company or an individual. Currently, there are many Companies that apply for scientific advice around issues involving: a) the patient population (high unmet medical needs), b) clinical practice (comparator), c) rarity (limitation of sample size, multiple subtypes), d) statistical methods (study power, interim analysis), and e) study design (primary endpoints, homogeneous population, randomisation, cross-over). To date, 192 marketing authorisation (MA) applications have been filed: 140 received positive opinion, 10 received negative opinion and 42 were withdrawn. Out of 51 orphan drugs which are on the market, 21 asked for PA.

The rarity of these diseases often leads to an inability to investigate and provide comprehensive evidence on the product quality, clinical safety and efficacy during the registration evaluation process which may mean that approval has to occur via

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the exceptional or conditional approval marketing authorization mechanisms, i.e. the company is either able or unable (respectively) to eventually provide a complete evidence package.

During the Orphan Drug sessions all the relevant procedures have been examined: from the designation, through the “protocol assistance”, the designing of clinical trials (innovative approaches) and evaluation process during the centralised procedure.

Valuable experience from both the Regulatory Agency (EMA) and pharmaceutical industry has been illustrated outlining the current regulatory and R&D framework in the orphan drug field.

The need of a full application of the Orphan Regulation has been highlighted, claiming for a close collaboration with all stakeholders. Pharmaceutical industries should continue to work with regulators to generate appropriate evidence to support the use of novel medicines to treat these rare conditions and regulatory assessors also have to accept different approaches to ensure the protection of the patients’ interests.