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Regulatory Science Challenges – Encouraging Innovation Through an Adaptive Regulatory System

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Keywords: *Regulatory science, advanced therapies, early access, PRIME scheme, medical device*

1. ATMPs – a new era

A boy from Hungary, Zente, was one and a half years old when the crowd-funding campaign to finance his life-saving medicine Zolgensma concluded with a happy end. He was the third European patient that received the new gene therapy, which replaces the function of the missing or nonworking survival motor neuron 1 (SMN1) gene with a new, working copy of a human SMN gene that helps motor neuron cells work properly and survive. From a European perspective, it has been almost 15 years by now since regulatory framework for advanced therapy medicinal products (ATMPs) had been established to ensure the free movement of these medicines within the European Union, to facilitate their access to the EU market, and to foster the competitiveness of European pharmaceutical companies in the field. Zolgensma has been approved in the EU in May 2020. The FDA expects it will be reviewing and approving up to 20 cell and gene therapies each year until 2025. Rapid development of technology and better understanding of the manufacturing challenges are not the only prerequisites of the growth. Assessment of products like Zolgensma requires very specific knowledge and often an adaptive approach from regulators. They have to gain enough experience and need to be able to summarize knowledge in guidelines that would help developers of products that are substantially different from traditional medicines. FDA issued seven new guidelines in January 2020, in which, for example, they highlight the importance of long-term follow-up for gene therapies that offer one-time fix for inherited diseases and where pre-market studies may have limited value.

2. Regulatory tools

These examples may already show that rapid change in technology leads to new kinds of medicines that require a properly adapted regulatory system. Patients would expect state-of-the-art medicines within the shortest possible time frame, however, authorities are traditionally more cautious. Still, there are several various initiatives from the EMA and the FDA to foster early access to medicines. Some of these have been available for a longer time. EMA's accelerated assessment reduces the timeframe for review of innovative applications of medicines with major public health interest. Conditional marketing authorisation grants authorization before a complete dataset is available, and compassionate use allows the use of an unauthorized medicine for patients with an unmet medical need. A more recent regulatory tool of EMA is the priority medicines scheme (PRIME) that aims to enhance support for the development of medicines that are expected to make a real difference to patients. Early dialogue between EMA and the developers is a crucial part of the tool, together with accelerated assessment and continuous scientific advice and protocol assistance. Up to now, 282 applications for PRIME eligibility have been assessed by the CHMP of which 95 have received a green light. Most of the applicants are small and medium size enterprises, and the major therapeutic area is oncology. FDA has similar programs, such as the Fast Track, Breakthrough Therapy and Priority Review designations, and is also aiming to facilitate and accelerate development and marketing authorization of key medicines. By 2018, about 70% of new drug approvals by the FDA were expedited, compared to about 50% in 2010. The result is a growing pro-

portion of medicines authorized with less pre-market evidence, a trade-off, that most patients with fatal or debilitating disease would likely accept. Nevertheless, conditional approval requires a strong post-marketing attention from regulators, and lack of enough evidence sometimes leads to difficult decisions. In April 2019 a fast-tracked cancer drug, Lartruvo was withdrawn because a large study was not able to prove a favourable benefit-risk profile, which was established previously on a smaller patient population. The regulators approach is not expected to be changed, but experience from such cases would gradually be built into the decision-making process. In addition to this, real world evidence (RWE) and patient recorded outcomes may also help in decision making.

3. Digital revolution

The rapid development of biotechnology is not the only area where an adaptive regulatory approach is needed. Digital medicine is a new field, as smartphones and sensors open up new ways of generating data. For example, collecting and analysing RWE seems to be a good solution for single arm studies where randomized trials are not feasible. FDA has approved easy-to-use devices that are able to track several physiological systems of our body, which in turn can give a boost to developments in this field.

In addition to these “simpler” devices, digital revolution in terms of artificial intelligence (AI) and cognitive machine learning is another challenge that our regulatory systems should tackle. It has been recently announced that a new drug candidate, a long-acting and potent serotonin 5-HT_{1A} receptor agonist, which was created using an artificial intelligence platform, will enter into clinical study. There are also numerous radiological applications based on AI, including computer aided-detection and diagnosis software, where images are analysed, and clinically relevant findings suggested to aid diagnostic decisions.

Many of these new developments require a tailored approach from regulators to find a way for authorization within the existing regulatory framework. The fact, that many of these new developments are carried out by academic research groups or small companies without extensive regulatory experience, adds an extra layer of difficulty. To meet this challenge, EMA and the Heads of Medicines Agencies have established the EU-Innovation Network, to support medicine innovation and early development. As a milestone of its function, beginning in 1 February 2020 a pilot for simultaneous scientific advice is starting, where the applicants will receive a consolidated advice from the participating agencies. Innovative products often require specific expertise; therefore this new form of advice is also extremely beneficial for regulators as they are able to learn from each other and broaden their knowledge.

4. Conclusions

The rapid development of pharmaceutical and digital technology requires a concerted action from all stakeholders. Or, as we all experience, a global pandemic can be an important driving force of the evolution of regulatory policies. Appropriate usage of currently available regulatory tools and a continuous discussion between academia, industry and regulators would be the only way to ensure quick access to state-of-the-art, safe and efficacious medicines, and medical devices. It is clearly shown currently by the concerted action of various stakeholders and series of rolling reviews which led to the expedited authorization of COVID-19 vaccines.

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