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Review

From molecule to market access: Drug regulatory science as an upcoming discipline ☆, ☆☆

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ABSTRACT

Regulatory science as a discipline has evolved over the past years with the object to boost and promote scientific rationale behind benefit/risk and decision making by regulatory authorities. The European Medicines Agency, EMA, the Food and Drug Administration, FDA, and the Japanese Pharmaceutical and Medical Devices Agency, PMDA, highlighted in their distinct ways the importance of regulatory science as a basis of good quality assessment in their strategic plans. The Medicines Evaluation Board, MEB, states: 'regulatory science is the science of developing and validating new standards and tools to evaluate and assess the benefit/risk of medicinal products, facilitating sound and transparent regulatory decision making'. Through analysis of regulatory frameworks itself and their effectiveness, however, regulatory science can also advance knowledge of these systems in general. The comprehensive guidance that is issued to complete an application dossier for regulatory product approval has seldomly been scrutinized for its efficiency. Since it is the task of regulatory authorities to protect and promote public health, it is understood that they take a cautious approach in regulating drugs prior to market access. In general, the authorities are among the first to be blamed if dangerous or useless drugs were allowed to the market. Yet, building a regulatory framework that is not challenged continuously in terms of deliverables for public health and cost-effectiveness, might be counterproductive in the end. Regulatory science and research can help understand how and why regulatory decisions are made, and where renewed discussions may be warranted. The MEB supports regulatory science as an R&D activity to fuel primary regulatory processes on product evaluation and vigilance, but also invests in a 'looking into the mirror' approach. Along the line of the drug life-cycle, publicly available data are reviewed and their regulatory impact highlighted. If made explicit, regulatory research can open the door to evidence based regulatory practice and serve the regulator's contribution to innovative drug licensing today.

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1. Introduction

Drug development today is a time-consuming and costly process. It takes on average approximately 10 years, and industry analysts estimate 1.8 billion US dollars from the stage of drug discovery to market authorization (Paul et al., 2010). Drug developers are required to comply with a series of rules and regulations that have been issued from the moment regulatory authorities were assigned with the task to protect and promote public health by deciding on market authorization. In the Netherlands, the Medicines Evaluation Board, MEB, was installed in 1963 and catalyzed by what is known as the thalidomide drama (www.lareb.nl). For many years, drug licensing took place at the national level with its own rules and procedures, and similar drugs could be on the market in different European countries with different indications and safety monitoring systems. The European Medicines Agency, today coined as EMA, was established in 1995. One of its first tasks was to establish harmonized drug licensing across the EU member states; free trade of pharmaceuticals would not be understood when products in one country would have a different label compared to the other. At the same time, it was decided to start licensing certain products through a centralized procedure, meaning, once approved, the drug is authorized in all member states at once. Compulsory for this procedure are certain disease area's such as HIV/AIDS, neuro-degenerative disorders, cancer, cardiovascular disease and diabetes, (auto)immune diseases, viral diseases, as well as advanced therapy- and orphan medicines. To facilitate this process, European regulatory guidelines were drafted at all levels of the drug development process, i.e. quality, non-clinical and clinical. These guidelines reflect a harmonized, informed approach affecting all EU member states. Contrary to directives, the guidelines have no direct legal basis, rather they offer a regulatory framework to ascertain good quality dossiers to be evaluated for marketing approval. Currently, the number of regulatory guidelines exceeds 600 (www.ema.europe.eu), and to find one's way through them has become complex for both drug developers and regulators.

Obviously, over the past years, the system's efficiency has been questioned and even criticized in relation to hampering or delaying access to new medicines by maintaining unrealistic hurdles for innovative drug development (Schellekens et al., 2011; Nutt et al., 2011). Yet, regulatory authorities are among the first to be blamed when ineffective or unsafe drugs enter the market. To that end, they rather take a cautious approach. They are often caught between a degree of uncertainty that is inherent to pre-marketing drug assessment and the anticipated manageability of post-marketing safety events on the one hand and a community's medical needs on the other (Raine et al., 2011; Eichler et al., 2011).

It is for this reason that the MEB has developed a keen interest in regulatory science in the direct context of the European licensing system, but also with extensive collaboration with other regulatory communities across the world. In the present review the MEB's regulatory science work is discussed and put into perspective of both safeguarding public health and promoting innovation.

2. Drug development and regulation over the life cycle

In Europe, the drug regulatory system is organized differently as compared to the US. Drug developers have to build their dossiers according to the EU Directives, but they are rather free in the way they choose their development plan. The many regulatory guidelines in place are a means to advise drug developers rather than to prescribe. They offer guidance to build a dossier with sufficient data of good quality that allow an informed benefit/risk assessment. Usually, companies start interacting with regulatory authorities at the time they start the clinical program, which is approximately 4 years prior to finalizing the dossier (Fig. 1).

During that time companies can apply for an orphan status of their product when eligible according to the inherent orphan definitions and requirements (www.ema.europe.eu). They can request scientific advice from national authorities and the European agency, which is a procedure that offers the opportunity to check on guidelines and discuss those issues that are not covered or new and upcoming. European licensing is therefore a procedure of checks and balances where companies take the lead in regulatory dialog. Over the years these dialogs in the form of scientific advices increased tremendously and have been proven useful (Regnstrom et al., 2010). However, the list of requirements for the application dossier increased as well. EU legislation has broadened its horizon towards children, advanced therapies including gene- and cell-therapy and tissue engineering, and, more recently, intensified marketing surveillance. After adoption of the Pediatric Regulation in 2007, companies have to submit, at the time of licensing, a pediatric investigation plan, PIP, covering quality aspects such as proper formulations and dosing forms for children and the clinical data that can not be extrapolated from adults. Risk Management Plans, RMP's, are extended, and Risk Minimization Activities, RMA's, to be monitored post-approval over the drug life-cycle. In the end, the Committee for Medicinal Products for Human Use, CHMP, has to give an opinion about the benefit-risk of products with a claim of indication for use.

The life-long monitoring of drug safety, and the possibility of adding post-approval data to the dossier, enables continuous benefit-risk (re)evaluation, which will be the standard procedure in the years ahead. In such a changing environment, it is of upmost importance to search for strategies that keep the system manageable, efficient and affordable for both regulators and industry. Initiatives to this extend are taken by the regulatory field itself (Ehmann et al., 2013). Drug development and regulation over the life-cycle is expected to shift slowly towards a more adaptive approach and thorough dialog not only between regulators and industry, but between patients, medical practice and society as well.

3. MEB's regulatory research

Over the past years, the MEB as one of the national authorities of the 28 EU member states, supported regulatory research in close collaboration with universities and other scientific institutes,

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