

Regulatory science: Regulation is too important to leave it to the regulators

On 19 December 2018, the European Medicines Agency (EMA) published its draft "Regulatory Science to 2025" strategy for a 6-month public consultation. In this EMA publication, regulatory science has been defined as "the range of scientific disciplines that are applied to the quality, safety and efficacy assessment of medicinal products and that inform regulatory decision-making throughout the lifecycle of a medicine" Earlier in 2011, the US Food and Drug Administration (FDA) issued a similar strategic plan for regulatory science for advancing its regulatory mission. Although the EMA plan is at the moment writing this draft for public consultation, both plans encompass elements of (1) enforcing regulators keeping up with the most recent science in order to enable high-quality and critical evaluations of the benefit-risk, (2) innovation in methods and standards for the evaluation of quality, safety, and efficacy of medicinal products throughout their product life cycle, and (3) a broad arrange of activities related to reaching out to stakeholders (ie, patients and health care professionals), enabling innovation, and studies into the question whether regulatory systems really deliver in terms of ensuring patient safety, safeguarding public health, and innovation.¹ Optimization of regulatory science is not restricted to Europe or to the United States. Also, Japanese regulators have explored relevant thinking pathways on how society's needs and values can be translated into scientific requirements to the evidence industry has to deliver at the moment they file a new drug application or when a product is at stake in case of a post-approval safety concern.²

A key aspect of medicines regulation is addressing questions like "what justifies approval of a new product or keeping an existing product on the market?" The typical response to that question will be "scientific evidence," and virtually, nobody will argue against this. But reality is complex. How much evidence? And what kind of evidence? Is 4 months PFS gain while no OS data are available yet in case of a rare, life-threatening cancer enough evidence or not? And how to justify a negative decision? In such situation, there is always the risk of a type I error, ie, a decision to approve a product is made but turns out to be wrong, too premature. These types of errors are the nightmare of every regulator. But we should not forget the risk of a type II error. A decision to approve the product is not made; ie, the application is rejected and turns out to be too precautionary, too risk averse. Regulators tend to be on the safe side when there is substantial doubt about the evidence package, very often for good reasons, but not always. There is also increasing awareness of the possible drawbacks

of being too risk averse in the interest of giving patients access to new promising therapeutic options.³

Reality of regulatory decision making shows that this is not always a straightforward yes or no. Scanning the EMA website for European public assessment reports (EPARs) makes this very visible in situations where products are approved on the basis of majority votes and not on consensus view. Obviously, individual members of the CHMP come to different conclusions on basis of the same scientific data, even after lengthy and in-depth discussions at the EMA. The same we see with certain dossiers at the FDA and other regulatory jurisdictions. We may expect that the future will be even more challenging given new and on the edge advances in drug discovery and development, including cell and gene therapies. It is one of the aims of regulatory science to disentangle the dynamics of such decision-making processes, to understand which factors contribute to a certain outcome and to find out what evidence is needed to make an informed and justifiable decision. Here, regulatory science includes behavioral sciences, decision theory, and tapping on innovation science. But apart from regulatory decision making, there is also the array of questions related to the regulatory system as a whole, including how to align with health technology assessment (HTA), dialogue with civil society, and the flip sides of regulatory incentive systems to stimulate industry investing in, for instance, orphan or pediatric medicines.⁴ On the latter, we see increasing public concern that such incentive systems may result in high priced medicines and complexities in patient access. Regulatory science should have informed impact and to a balanced rethink of how to ensure a regulatory and business ecosystem for the industry that is not a free ticket for perverse pricing and at the same moment avoiding that the baby, ie, these systems have also delivered new therapeutic options, is not thrown out with the bathwater.

In conclusion, regulatory science is about studying and adding to regulatory systems, decisions, and impact on public health in a complex policy, legal, and business environment of bringing efficacious and safe medicines to the patient. This Journal also has echoed extensively the importance of regulatory science for drug development, clinical evaluation, and usage in various ways. The number of accepted papers with direct and indirect links to regulatory science has increased over the last 5 years; the Journal has started a new series of reflections on EMA guidelines and regulatory documents.⁵ Moreover, the most critical part of every regulatory dossier, ie, what clinical benefits have been

shown in studies of a certain product, is the *home* of clinical pharmacologists in all its aspects. In determining the best study design, selecting clinically relevant endpoints that matter, and finding the most appropriate dose, clinical pharmacologists, for sure not exclusively, are in the forefront of navigating a trial to the best outcome ready for regulatory decision making. And increasingly, we see non-randomized data (eg, registries and real-world data) coming into the field, with all the inherent challenges of methodological robustness and power of justification a regulatory decision.

COMPETING INTERESTS

H.G.L. has been a chair of the Dutch Medicines Evaluation Board (MEB) and a member of the EMA Committee for Medicinal Products for Human Use (CHMP).

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