

## **In silico trials and drug approval process: where are we?**

Flora Musuamba Tshinanu<sup>1, 2</sup>

<sup>1</sup>Federal Agency for Medicines and Health Products, Brussels, Belgium

<sup>2</sup>University of Lubumbashi, Lubumbashi, DR Congo.

Marketing approvals of (new) medicinal products (and combinations) generates large interests of both patients in need of new medicinal therapies and the sponsors (big pharmaceutical industry, SMEs, and academia). Before a new medical product can be used on humans in a country, it must be approved for that use by the relative Regulatory Authority of that country. In USA, this will be the remit of the Food and Drug Administration (FDA) drugs and medical devices whereas in the European Union pharmaceuticals are approved by the European Medicine Agency (EMA) mostly and by national competent authorities to a lesser extent. The approval of medical devices is delegated to the member states, through selected notified bodies.

Consequently, regulators have to find the appropriate balance between the need to ensure that decision-making is based on scientifically valid data and the need for access to the new medicines is considered.

To obtain approval for a (new) medicinal product the sponsor must submit to the regulator evidences of a favourable risk/benefit balance based on available efficacy and safety data.

Historically, the demonstration of drug's safety and efficacy was mostly based on evidences obtained experimentally, either in vitro (e.g. testing the efficacy of a new chemotherapy in a tumour cells culture, or the fatigue strength of a hip replacement in material testing machine), or in vivo on animals and on human volunteers or patients in controlled clinical trials and statistical analyse thereof; in silico methods were initially limitedly used.

However, a concerning issue has been acknowledged by almost all the stakeholders that, over the last decades, there has been a trend of rising research and development (R&D) expenditures, but no increase in the number of newly developed medicines submitted to regulatory agencies. One of the reasons put forward by pharmaceutical companies for the decrease in the efficiency of drug development and approval is that regulators are overly cautious, resulting in rising R&D expenditures and long drug development timelines.

At the EMA, it has been acknowledged over the years that efficient drug approval process would benefit for early and frequent interactions with drugs' sponsors through establishment of formal procedures and offices for this purpose. To date, these interactions include ITF briefing meetings, scientific or qualification advice, qualification opinion and marketing authorization applications (including pre-submission and explanatory meetings) as summarized below.



It is also acknowledged that clinical trials become increasingly complex, large, and expensive. The traditional approaches of drug development based on large randomized controlled trials faces big issues to be implemented in situations, despite a high unmet medical need, namely orphan indications, drugs for very young children and the elderly, and slowly evolving diseases, etc. Biomarkers, sophisticated imaging methods, patient-reported outcomes, combined with novel and innovative methodologies such as modelling and simulation (M&S) and in silico approaches play an increasingly important role in drug research and development and have the potential to deliver new medicines to the right patient faster and at a lower overall cost than today, also by ensuring that resources reserved for the drug-development programs are diverted.

M&S and in silico approaches are now routinely used by pharmaceutical companies and drug sponsors for example for key decision making on the most promising drug development programs in their pipelines and for moving to key steps of their projects and to characterize some important features of their different studies. M&S are now also increasingly used to identify the most sensitive subgroups of patients for both drug efficacy and safety, thanks to systems medicines and systems pharmacology models. The above listed applications are contributing to faster access to better quality medicines for patients.

Regulators therefore need not only to provide guidance, advices and recommendations on the acceptability of these methods for regulatory submissions but also to adequately use them in their decision making process. The involvement of M&S and in silico approaches in the different regulatory procedures will be discussed through concrete examples.

It will be shown that currently, the biggest challenges are coming from unreliable and low quality and immature models with poor predictive performances in their context of use that bring discredit and hamper the acceptability of models by people without quantitative background in particular.

Moreover the fact that good standards for evaluation of some models in some particular context of use are currently lacking is also one of the current big challenges.