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# The New EU Legislation on Pharmacovigilance and Changing Models for Drug Development

In a recent issue of *Drug Safety*, Borg et al.[1] reviewed the new EU legislation on pharmacovigilance and compared it with the legislative framework currently in force. The authors note that, on a range of topics, the new legislation provides improvements and should, overall, lead to a strengthening of the EU pharmacovigilance system. In this context it seems natural to ponder on its potential use for meeting a challenge rarely discussed within the pharmacovigilance community, which by its nature focuses on the post-approval phase of a drug's life cycle.

Against a backdrop of declining productivity within the pharmaceutical industry in recent years, the traditional paradigm for drug development is now challenged.[2] The factors underlying the current predicament of the research-based industry are probably multifaceted and remedial efforts to advance the efficiency of drug development involve several areas. In order to lower the costs of clinical development, a number of new concepts are now being evaluated and increasingly often applied.[3] For example, modelling and simulation have been shown to be useful for gaining a better understanding of biological processes and can help in optimizing clinical trial design, dose selection and development strategies. In early development, external information can be used in modelling and thereby increase the efficiency of the development process. In later phases of development, simulation can make clear how different study designs affect the outcome and probability of success, thereby guiding development strategy. Furthermore, in an attempt to move from the traditional development paradigm with sequential phases to a more integrated development model, new flexible trial designs (i.e. adaptive trials) are now being proposed. In these trials, accumulated knowledge is used to modify and improve the study design, in a pre-planned manner without undermining the study's validity or integrity. In this way, these new study designs can potentially compress timelines, and improve dose and regimen selection. For example, an adaptive trial can assign a larger proportion of patients to treatment arms that are performing well and drop arms that are performing poorly, thereby reducing the number of patients exposed to non-viable dosing regimens. In later development phases, adaptive designs can help determine whether a trial should be terminated early for futility and also make sample-size adjustments at interim timepoints to ensure that the trial is adequately powered. It may also be possible to enrich a study population by altering inclusion or exclusion criteria based on interim data. Lastly, a better understanding and increased use of various biomarkers hold the promise of a more optimal recruitment into clinical trials. Patients most likely to respond to treatment can preferentially be included, thereby reducing the number of patients needed to demonstrate efficacy. Biomarkers can also be used as surrogate endpoints, in which case it is essential that research can establish a close correlation between the biomarker and late-stage outcomes.

It has to be understood that the focus of the abovementioned approaches is to increase efficiency in demonstrating benefit, and their consequences for the safety evaluation of a drug are unclear. However, it seems reasonable to assume that smaller and shorter development programmes will reduce the volume of clinical safety data available at market launch. If that turns out to be the case, more research is needed so that pharmacovigilance can be provided with new tools and strategies.[4,5] Consequently, those involved in pharmacovigilance need to raise their awareness of the ongoing transformation of the current development model, and reflect on its potential implications for post-approval surveillance. Furthermore, with the advent of the new EU legislation on pharmacovigilance, European regulators should consider how the regulatory tools provided in the new legislation can be applied in order to ensure the safe use of drugs coming from a changed drug development model.

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# The Authors' Reply

We read with interest the letter by Torbjörn Callréus[1] regarding our recent review article on the new EU legislation on pharmacovigilance.[2] Our purpose was to provide an up-to-date, comprehensive review of the complex legislative framework on EU pharmacovigilance and how this is going to change once the new legislation is fully implemented in the EU by Member States, the Commission and the European Medicines Agency. We believe our review will help all stakeholders (regulators and industry) understand the new issues when confronted with the complex legislative changes and their ramifications on current practices.

We agree with the author's comments on the paradigm shift in drug development, whereby new concepts applied in clinical development (to achieve faster access to medicines and lower the costs of clinical development) are expected to result in a reduction of clinical safety data available at the time of market launch. However, EU regulators are not entirely new to evaluating medicines with limited safety data and having to grant a drug approval, since implementation of Regulation 726/2004/EC[3] (setting up the centralized EU marketing authorization procedure) introduced conditional marketing authorizations and marketing authorizations granted under exceptional circumstances where, in both cases, limited clinical safety data are available. Thus, monitoring of theses drugs on the market utilizing the current legislative framework by annual reassessments, risk management plans and periodic safety update reports are perceived to be effective in monitoring the benefit/risk of approved drugs under these conditions. It is our opinion that the new legislation on pharmacovigilance will allow further regulatory tools (such as the intensely monitored list of products in the EU, post-authorization safety studies, post-authorization efficacy studies and risk management plans as legal conditions of the drug approval) than are currently available to be able to ensure the safe use of drugs coming from a changed drug development model.

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The views expressed in this article are the personal views of the authors and may not be used or quoted as being made on behalf of, or reflecting the position of, any national competent authority, academic institution or the Permanent Representation of Malta to the EU.

The authors declare that they have no direct or indirect potential conflicts of interest.

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