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Review Article

Panvigilance: Integrating Biomarkers in Clinical Trials for Systems Pharmacovigilance

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Abstract

Drug safety and pharmacovigilance are rapidly changing with biomarkers and new technologies such as artificial intelligence. However, we need new ideas and application contexts for integration of biomarkers and emerging technologies in modern pharmacovigilance. A new concept, panvigilance, has been recently introduced for proactive ''stress testing'' of new drug candidates in panels of patients or healthy volunteers identified by biomarkers, and who are situated in population edges in terms of pharmacokinetic (PK) and/or molecular target interindividual variability. Panvigilance aims to provide upper and lower bound estimates for drug performance under conditions that mimic population edges. Subsequently, it becomes easier to extrapolate pharmacovigilance signals with regard to individuals who reside in between the population edges. In this expert review, we explain that the prefix ''pan,'' meaning everything or all, refers to the three-pronged panvigilance goals to (1) decipher the full population scale variability in medicinal product PKs and molecular target variability, (2) empower forecasting of pharmacovigilance signals within and across populations through knowledge of biomarker variations worldwide, and (3) integration of pharmacovigilance signals across government ministries, civil society organizations, and other stakeholders through, for example, institutional innovation such as centers for panvigilance. We note that panvigilance and pharmacovigilance are complementary, and underscore the added value of panvigilance for global clinical trials. Panvigilance offers a new opportunity for meaningful biomarker application in clinical trials beyond traditional contexts such as personalized medicine. In sum, panvigilance is a systems approach to pharmacovigilance and poised to innovate risk governance in medicinal product development and clinical trials.

Keywords: panvigilance, pharmacovigilance, clinical trials, adverse drug reactions, drug safety, centers for panvigilance

Toward Next-Generation Pharmacovigilance

Drug and medicinal product development is a high-risk venture. Historically, the first pharmaceutical companies benefited from the textile and synthetic dye industries of the 19th century that made available, as spin off products, new compounds and chemicals as raw materials for pharmaceutical innovation. Modern day drug development scholars face challenges and uncertainties quite different than the past centuries, however. Two related challenges continue to stifle pharmaceutical and medicinal product innovation in the current era of biomarkers and personalized medicine.

The first challenge, and chief among the medicinal product development risks, is the uncertainty and unknowns on the pharmaceutical innovation trajectory, particularly with regard to drug safety and efficacy (Kalow et al., 1999). The current paradigm of drug development tests medicinal products and medical devices in clinical trials before routine use in the general population. The collective sample size in clinical trials does not exceed, however, few thousands at most, whereas medicinal products, once introduced in the clinic, are often used in many thousands and millions. Therefore, a corollary of the present pharmaceutical innovation paradigm is that the common adverse drug reactions (ADRs) are identified in clinical trials but less common and rare ADRs, and the broader range of drug-related problems are only detected once a drug is set free for use outside the realm of controlled clinical trials, and the diversity and size of the population exposed to the drug increase to many thousands and millions.

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Over the past decades, biomarkers have met with mixed enthusiasm in the pharmaceutical industry (Ohashi and Tanaka, 2010; Selleck et al., 2017). Although personalized medicine, reduction in development timelines, and costs have been often noted as some of the key application contexts and added value of biomarkers (Ohashi and Tanaka, 2010), pharmacovigilance is another important biomarker application in global clinical trials.

The second challenge among the medicinal product development risks relates to the ways in which developing and low- and middle-income countries (LMICs) can contribute to drug, medical device, and other medicinal product innovation such as vaccines, nutrition, traditional and herbal medicines, and cosmetics, among others. We suggest that there is much that can be accomplished in LMICs beyond human subjects recruitment and importantly in ways that contribute to responsible innovation and integration of biomarkers in clinical trials and global pharmacovigilance.

The concept and practice of pharmacovigilance are pertinent as we seek answers to both of these global drug development challenges. Pharmacovigilance is a broad field of scholarship, concerned not only with pharmaceuticals but also with the broad range of medicinal products above, not to mention drug–drug, drug–herbal medicine, and drug–food interactions (Şardaş et al., 2014; WHO, 2004).

The World Health Organization (WHO) defines pharmacovigilance as ''the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems'' (WHO, 2006). Anyone interested in pharmaceutical and health product responsible innovation takes notice of pharmacovigilance as a critical concept and practice for public health and innovation policy. The importance of pharmacovigilance for safety monitoring of medicinal products has been emphasized by various national and international organizations including the WHO as well as various databases that support pharmacovigilance efforts worldwide.

Yet, ADRs and other medicinal product-related problems continue to rank as leading causes of morbidity and mortality in many industrialized countries as well as LMICs. In addition, measuring medicinal product safety in a comprehensive manner on a national scale is challenging.

Nearly a decade ago, we have raised the issue for the need toward next-generation pharmacovigilance, and specifically, newer concepts, practices, and technologies that can help better design national pharmacovigilance systems so that drug toxicity and/or resistance signals are detected earlier, and in a more mechanistic manner to permit population level extrapolations (Şardaş, 2010). Despite piecemeal advances toward a systems approach to pharmacovigilance, the field still lacks the resources and rigorous conceptual models to incorporate biomarkers and other new technologies. Systems pharmacovigilance would complement other systems scale efforts for drug safety such as spontaneous reporting of ADRs, medicinal product quality deviations, types of drugs associated with ADRs, and their severity for every country.

Hence, we pose the following question: what are the ways in which pharmacovigilance concepts and practices could be innovated using biomarkers so as to expeditiously forecast and govern the risks and uncertainties attendant to medicinal product development, and their efficacy and safety, in particular?

Panvigilance

A new conceptual framework for ''stress testing'' and regulation of medicinal products has been recently proposed, namely, panvigilance (Özdemir and Endrenyi, 2019). The idea of panvigilance is based on stress testing of new drug candidates and other products in clinical trials, specifically, in panels of individuals identified in a mechanism-oriented vision by extremely discordant biomarkers (EDBs) and who display pharmacokinetic (PK) and/or pharmacodynamics (PDs) attributes situated in population edges (Fig. 1).

Accordingly, it has been noted that ''as with aircrafts or automobiles tested in wind tunnel experiments, our main premise is that drugs, too, warrant 'stress testing' proactively so as to identify, early on, their performance under conditions that mimic the population extremes (edges) in regards to distribution of PK traits and molecular drug targets'' (Özdemir and Endrenyi, 2019).

Importantly, stress or road testing of new drugs in the case of panvigilance helps establish the upper and lower bound estimates for drug performance in case studies of EDBs conferring very high or low drug exposure, and very low or high values of drug potency (EC_{50}) and efficacy (E_{max}). Once equipped with knowledge of performance of a drug candidate in population edges for PK and molecular target variability, it becomes easier to extrapolate drug safety signals with regard to individuals who reside in between the population edges (Fig. 1).

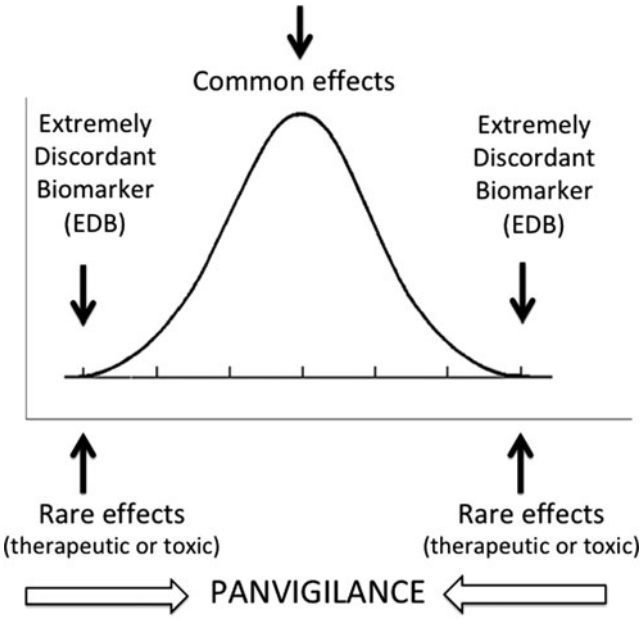

FIG. 1. Panvigilance for pharmaceuticals and medicinal products' risk forecasting and regulation. Panvigilance offers the advantage of forecasting the signals on unknown drug effects, be they adverse, toxic, or therapeutic, by prioritizing pharmacokinetic and pharmacodynamic analyses in population edges as defined by biomarkers. Importantly, the direction of discovery for drug effects is ''from rare and less common to common'' in the case of panvigilance. This contrasts with traditional pharmacovigilance that detects, first, common drug effects in controlled clinical trials, followed by less common and rare drug effects as exposure to the new product increases in the target population. Adapted from Özdemir and Endrenyi (2019).

Another extension of panvigilance, one that we wish to underscore in the present article for global clinical trials and pharmacovigilance, is that numerous biomarkers presently exist whose distributions in world populations are already known. In the event a pharmacovigilance signal is detected, in clinical trials or in postmarketing phase, one can extrapolate such early signals from one population to another by knowledge of the differential distribution of biomarkers worldwide. For example, if a new molecular entity is found to be associated with increased drug exposure and early signs of toxicity in persons with poor metabolism for that drug clearance pathway, cross-population extrapolations can be potentially made for risk assessment and governance across nation state borders. Such biomarker-informed pharmacovigilance signal detection and extrapolation across the national borders and geographies are possible with panvigilance.

Future institutional innovation is also necessary, for example, centers for panvigilance and global clinical trials, which can effectively identify the biomarkers that confer very high or very low functional capacities for various PK pathways and/or molecular targets. Such new organizations and centers could then design, oversee, and implement panvigilance clinical trials for the purpose of early signal detection on drug safety and efficacy, not to mention extrapolation across populations. Panvigilance centers can be part of the National Ministry of Health Clinical Trial Departments and Pharmacovigilance Centers in cooperation with other ministries such as agriculture and global actors for pharmacovigilance and drug safety (Fig. 2).

EDB-guided clinical trials can be implemented in phase 1 and phase 2 studies of new drug candidates so as to inform large scale phase 3 trials (Özdemir and Endrenyi, 2019). Moreover, we note that drugs that are already in routine use can also benefit from EDB-guided phase 4 clinical trials as the use and exposure of a new drug are scaled up worldwide and in various populations. Caution is necessary, however, in implementing clinical trials informed by EDBs to ensure clinical trial participants' safety, and so that single dose studies are advisable as an initial entry point for panvigilance studies before multiple dose studies.

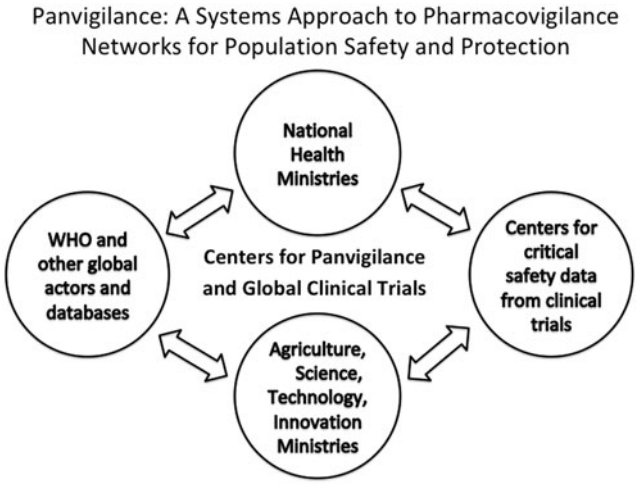

FIG. 2. Panvigilance: A systems approach to pharmacovigilance and risk governance.

To place the panvigilance and EDB-guided drug development into further context, it is noteworthy that the current traditional approach to pharmacovigilance signal detection is much slower. The inclusion of persons in population edges is left to the ''incremental and slow increase in the number of the drug-exposed population sample by non-mechanistic recruitment of subjects'' (Özdemir and Endrenyi, 2019). In parallel to panvigilance, practices and public policies related to more effective pharmacovigilance need to be implemented as well so that the number of spontaneous reports increases. In contrast, not every side effect is a result of a drug's PK or PD attributes. Other therapy-related issues such as drug–drug and drug–food interactions or substandard quality of the drug should never be ignored in any assessment of ADRs (Şardaş, 2010).

Conclusions and Outlook

In so far as the integration of panvigilance, global clinical trials, and biomarkers is concerned, as already highlighted, many of the drug metabolizing enzymes and molecular drug targets display marked population and geographic variation in gene expression and/or prevalence of polymorphisms that impact their function at a protein level. We suggest, therefore, that institutional innovation such as establishing centers for panvigilance and global clinical trials in academia, governments, think tanks, and/or the industry at large would be timely.

As the prevalence of biomarkers varies worldwide across populations, such institutional innovation would permit rational design of global clinical trials of novel health products in ways that are informed by the latest biomarker discoveries and access to panvigilance testing globally. This is important so that the word ''global'' in clinical trials does not come to be understood narrowly as an effort to increase the statistical sample sizes in clinical trials but also allow and empower LMICs, their scientists, and diverse populations to engage in the art and science of drug development and biomarker research. Adding value to global clinical trials with biomarkers need not be limited to the end goal of personalized medicine but should also include moving toward systems pharmacovigilance and panvigilance.

The field of drug safety and pharmacovigilance is rapidly changing with the introduction of data science, new technologies such as artificial intelligence, machine learning, the Internet of Things, among others (Danysz et al., 2018; Davazdahemami and Delen, 2018; Özdemir, 2019a; Özdemir and Hekim, 2018). National Pharmacovigilance Centers are also gaining visibility worldwide (Ampadu et al., 2018). New ideas and concepts such as panvigilance that permit consideration of the full population range of PK and molecular target interindividual variation, and stress testing of new drug candidates in population extremes identified by biomarkers in diverse populations, can take global clinical trials to a greater scholarly realm and contribute to next-generation pharmacovigilance innovation.

Panvigilance and the traditional pharmacovigilance are complementary, and together they can help achieve greater quality in science broadly (Ravetz, 2016; Sarewitz, 2016), and drug safety and rational therapeutics specifically (Şardaş, 2010; Şardaş et al., 2014), thus, effectively integrating risk assessment and risk governance, biomarkers, and global

clinical trials scholarship. One way to accomplish this goal, as already suggested, is institutional innovations such as centers for panvigilance and global clinical trials that build on local strengths and under a sound vision of biomarker and drug development science and responsible innovation.

We shall underscore that panvigilance demands technology policies that are crosscutting, responsible, coherent, and responsive to uncertainties on the technology and innovation trajectories (Collingridge, 1980; Özdemir, 2019b; von Schomberg, 2013) across various government ministries such as the ministries of health, agriculture, science and technology within and across countries.

In sum, panvigilance and EDB-guided global clinical trials offer a systems lens on governance of pharmaceutical and medicinal product innovation, and warrant consideration as an integral part of the future efforts to ensure medicinal product population safety and efficacy.

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Author Disclosure Statement

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Abbreviations Used

ADRs = adverse drug reactions
EDB = extremely discordant biomarker
LMICs = low- and middle-income countries
PD = pharmacodynamic
PK = pharmacokinetic
WHO = World Health Organization