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Advancing Drug Safety Through Prospective Pharmacovigilance

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Abstract

Much has changed in a relatively short period of time. There is a raging debate over the level of evidence expected to first introduce a treatment to patients based on smaller, more adaptive data sets. Some argue for less data followed by postapproval follow-up, others for more adaptive clinical trial designs and end-point modification driven by patient-focused drug development and use of real-world evidence. The transition in both the review and postmarketing regulatory framework is happening in front of our eyes in real time.

To improve the ability of patients to receive high-quality, safe, effective, and timely care, better information via pharmacovigilance must be a priority as the world's many regulatory systems build the capacity to harness electronic health information to improve health, care quality, and safety. Globally, the widely variable ability of nations to build reliable regulatory systems (from precise review to robust pharmacovigilance) is a dangerous source of health care inequality.

Developing validated tools and techniques for "predictive pharmacovigilance" will assist all health systems in better understanding the risks and benefits of the medicines they regulate by understanding what should be happening once a new medicine moves from risk-benefit regulatory efficacy to real-world risk-effectiveness. This will be of particular utility for smaller regulatory agencies with fewer resources. By comparing preapproval predictive pharmacovigilance data, developing regulatory authorities will be able to better understand the potential gap between what was predicted and what was actually measured (via more traditional pharmacovigilance methodologies).

Predictive pharmacovigilance recognizes the value of understanding the imperfect reporting of real-world clinical use and that the absence of reporting is, in itself, an important postmarketing signal.

Keywords

pharmacovigilance, real-world evidence, artificial intelligence, expedited pathways

A New Era in Drug Development

Much has changed in a relatively short period of time. There is a raging debate over the level of evidence expected to first introduce a treatment to patients based on smaller, more adaptive data sets. Some argue for less data followed by postapproval follow-up, others for more adaptive clinical trial designs and end-point modification driven by patient-focused drug development and use of real-world evidence. The transition in both the review and postmarketing regulatory framework is happening in front of our eyes in real time.

Consider how the FDA has advanced its thinking (and guidance) for multiarm, multicompany clinical trials. The agency has outlined how developers of drugs targeting rare pediatric diseases can streamline their clinical development programs by collaborating. Officials want drug developers to consider teaming up to test multiple candidates in single trials, thereby cutting the number of patients who need to receive placebos.

Using Gaucher disease as an example, the FDA's draft guidance[1] shows how companies can team up and run multidrug clinical trials. These studies would enable multiple experimental candidates to be compared against a single control group, increasing the proportion of patients in active arms.

Other sections of the guidance propose the use of modeling and simulation to predict the effect of a drug in children based on prior performance in adults. Collectively, the FDA sees the proposals streamlining the development of drugs to treat rare pediatric diseases.[2]

According to Janet Woodcock, MD, director of the FDA's Center for Drug Evaluation and Research, "The FDA has drafted an approach to pediatric rare disease drug development

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that could eliminate the need for certain clinical studies and, when pediatric clinical studies are needed, could reduce the total number of patients who would receive a placebo instead of a potentially helpful drug."[3]

Problem or Opportunity?

When it comes to regulatory science and the broader issues facing the US Food and Drug Administration, there will always be significant gradations of nuance and ambiguity. "Predictability" is a trail that regulator and regulated must blaze together sometimes heroically and at other times with greater caution. While there is much debate and scholarly discussion on the issues pertaining to drug development and regulatory review, the debate on a more 21st-century approach to postmarketing surveillance is still in its earliest days.

Is Pharmacovigilance Changing With the Times?

In both the USA and the EU, proactive pharmacovigilance efforts by both regulators and pharmaceutical companies have escalated in recent times through (among other efforts) an increased use of real-world data, gathered and validated across multiple sources after a medicine has been approved.

In a world increasingly driven by outcomes reporting and Big Data, increasing amounts of patient-level information from individual consumers is not always synonymous with validated data. Despite the frustrating increase in the signal-to-noise ratio, artificial intelligence is becoming an ever-more significant source of potentially valuable electronically generated health care information.

Once considered "junk science," real-world evidence (clinical outcomes data not collected in conventional randomized controlled trials) is the new star on the precision medicine horizon and will help define the scope and strategies of 21st-century pharmacovigilance. Artificial intelligence (the theory and development of computer systems able to perform tasks that normally require human intelligence) will facilitate what the pharmacovigilance ecosystem lacks today—a coordinated and efficient systems for developing actionable evidence on safety and effectiveness. Such information will also prove crucial in pricing and reimbursement decisions and postapproval labeling updates. It could also impact a more progressive view of initial product labeling to present a more forward-looking "real-world" dynamic by moving beyond an exclusive view on "expectedness" to a more aggressive preapproval labeling dynamic based on a sponsor's premarket distribution and marketing strategies.

How will such new dynamics impact, for example, the European Union's 2012 pharmacovigilance legislation that created (among other things) rules for Post-Authorization Safety/Effectiveness Studies[4] (PASS/PAES). Postauthorization safety studies are carried out after a drug has been authorized to obtain further information regarding its safety or to measure the effectiveness of risk minimization measures. The PASS system is a valuable monitoring tool—but it isn't anticipatory. How can a PASS system be reconfigured to consider new, nontraditional data sets? How can we create a system (or update an existing one) to be predictive rather than purely reactive—because even the best pharmacovigilance systems are reactive. It's just that some are more sensitive than others. All this points out is that not only do we need to make existing designs better but that we need better designs.

We need to go beyond spontaneous reporting and design systems that provide informed, evidence-based "signal anticipation." This will require a more progressive view of data generated via social media and other sources that present challenging signal-to-noise obstacles.

To improve the ability of patients to receive high-quality, safe, effective, and timely care, better information via pharmacovigilance must be a priority as the world's many regulatory systems build the capacity to harness electronic health information to improve health, care quality, and safety. Globally, the widely variable ability of nations to build reliable regulatory systems (from precise review to robust pharmacovigilance) is a dangerous source of health care inequality.

There is so much data to utilize: patient medical history records, treatment data, and lately information coming from wearable health trackers and sensors. This huge amount of data must be analyzed not only to provide patients who want to be proactive with better suggestions about lifestyle, but also to serve providers with instructive pieces of information about how to design health care based on the needs and habits of patients, and provide regulators with not just more data but better data *in context*.

The Role of Artificial Intelligence

Artificial intelligence (AI) will have a huge impact from genetics to genomics, helping to identify patterns in huge data sets of information and medical records, looking for mutations and linkages to disease. There are companies out there today inventing a new generation of computational technologies that can tell doctors what will happen within a cell when the DNA is altered by genetic variation, whether natural or therapeutic. Imagine the predictive capabilities for pharmacovigilance.

For any of this to work—and especially in the world of pharmacovigilance—we must view artificial intelligence through the lens of 21st-century *interoperability*: the idea that different systems used by different groups of people can be used for a common purpose because those systems share standards and approaches.

We must also understand and embrace AI's abilities to make sense of nontraditional data derived from social media and other sources of spontaneous notification. Not only will AI provide the pharmacovigilance community with the opportunity to go beyond Drug Utilization Studies as the only tool and drug recalls as the only solution. Such a scenario becomes even more urgent when considering the current state of affairs relative to biologics (both innovator and follow-on). Current developmental

pathways are inefficient and insufficient to predict the risk profile of these medical products and issues surrounding similarity, indication extrapolation, and interchangeability only serve to highlight the need for a more predictive tool set.

Philip K. Dick wrote, "Reality is that which, when you stop believing in it, doesn't go away."

Inventing the Pharmacovigilance Future

A new era of medicines development and regulation requires both new approaches to pharmacovigilance and greater international collaboration and cooperation. To that end, we suggest an international effort under the tripartate chairmanship of the World Health Organization (WHO), the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), and the Council for International Organizations of Medical Sciences (CIOMS) to investigate, debate, and develop prototype programs for oncologic and other drugs approved via emerging and evolving expedited review pathways based on more sensitive premarket metrics of risk potential taking into consideration (among other variables) drug developer sales projections for both on- and off-label indications.

Based on these data sets, sponsor and agency would then develop a "Real World Pharmacovigilance Score (RWPS)"—a three-dimensional baseline prediction of likely adverse events based on projected volume and specific clinical use. Imagine what such a scoring mechanism might have taught public health authorities prior to the explosive event of the Vioxx imbroglio.

An *RWPS* is of particular value for innovative, costly oncology medicines, since their use is, in the majority, of an off-label nature. It will be an equally valuable tool for new biologics as well as for better capturing the safety and efficacy of both biosimilars and generic nonbiologic complex drugs (NBCDs). "Predictive pharmacovigilance" is a tool for both clinical value and value-based reimbursement.

The result of this program will be a design for validated tools and techniques for predictive pharmacovigilance design and implementation.

Conclusion

Developing validated tools and techniques for predictive pharmacovigilance will assist all health systems in better understanding the risks and benefits of the medicines they regulate by understanding what *should* be happening once a new medicines moves from risk-benefit regulatory efficacy to real-world risk-effectiveness. This will be of particular utility for smaller regulatory agencies with fewer resources. By comparing preapproval predictive pharmacovigilance data, developing regulatory authorities will be able to better understand the potential gap between what was predicted and what was actually measured (via more traditional pharmacovigilance methodologies).

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1. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM587660.pdf
2. https://www.fiercebiotech.com/biotech/fda-opens-door-to-multi-arm-multi-company-clinical-trials
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