21st Century Pharmacovigilance:

Intuition, Science, and the Role of Artificial Intelligence

In an environment of real world evidence, patient reported outcomes, expanding expedited and conditional review pathways for the treatment not only for cancers, but for a broad spectrum of serious and life-threatening diseases, we must care more than ever about pharmacovigilance via more regular and creative risk management plans to be sure, but also through a more diligent effort to understand just what "safety and surveillance" is about in the 21st century. At least part of the solution lies with something called “Artificial Intelligence.”

According to Dr. Bertalan Mesko, we are experiencing the Fourth Industrial Revolution, which is characterized by a range of new technologies that are fusing the physical, digital and biological worlds, impacting all disciplines, economies and industries, and even challenging ideas about what it means to be human. Healthcare will lead this revolution and artificial intelligence will be one of the major catalysts for change with actionable consequences.

Artificial intelligence has unimaginable potential. Within the next couple of years, it will revolutionize every area of our life, including medicine – and pharmacovigilance.

With the evolution of digital capacity, more and more data is produced and stored in the digital space. The amount of available digital data is growing by a mind-blowing speed, doubling every two years. In 2013, it encompassed 4.4 zettabytes, by 2020 the digital universe – the data we create and copy annually – will reach 44 zettabytes, or 44 trillion gigabytes.

Usually, we make sense of the world around us with the help of rules and processes that build up a system. The world of Big Data is so huge that we will need artificial intelligence (AI) to be able to keep track of it.

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

The broader question is about the future of Real World Evidence. 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.

21st century pharmacovigilance isn’t just about uncovering, reporting, and addressing adverse events associated with already approved and marketed
prescription medicines, rather it can be best described as the systematic monitoring of an “ecosystem” or in the words of the United Kingdom’s Medicines and Healthcare Products Regulatory Agency “Monitoring the use of medicines in everyday practice to identify previously unrecognized adverse effects or changes in the patterns of adverse effects; Assessing the risks and benefits of medicines in order to determine what action, if any, is necessary to improve their safe use; Providing information to healthcare professionals and patients to optimize safe and effective use of medicines; Monitoring the impact of any action taken.”

Ground Zero for a real-world evidence regulatory pathway will be Sentinel, the existing public/private program that uses a variety of databases to track, collect and analyze adverse event reports about drugs, vaccines and medical devices. But the tool set for using this new treasure trove of health care information is nascent and the tasks as are daunting as the opportunities.

Consider biosimilars. A key issue driving the development of 21st century regulatory PV activities is the need for updated post-marketing surveillance of biosimilars. Issues related to the particularities of biologics (sources, process, quality requirements and new safety profiles) require sophisticated new thinking. Fundamentally, all of the players in the pharmacovigilance ecosystem will have problems characterizing biosimilar issues since we don’t have an existing, validated predictive models of potential “hot spot” products, base ingredients or suppliers. Consequently, bio similar pharmacovigilance will have to evolve at the same time as new medicines are launched into this space.

Part of the solution to this post-marketing “indetermination” will certainly be strategies spear-headed by tools powered by artificial intelligence, and the first step should be to develop new epidemiological approaches based on a better understanding of the differences between the concepts of “generic” and “biosimilar.” We already understand there can be different safety profiles for generics (based on differing bioequivalence ranges, excipient and API sourcing, etc.).

When it comes to biosimilar PV activities, however, variability-induced iatrogenesis concerns, differences between batches by multiple manufacturers, and the elastic definition of “similarity” aren’t only questions of “safety profile,” but also of “concept.”

Artificial intelligence will facilitate what the pharmacovigilance ecosystem lacks today – a coordinated and efficient systems for developing actionable evidence on safety and effectiveness.

Today, the absence of these capabilities significantly impacts the public health by creating obstacles for patients and clinicians to receive the meaningful information they need to make informed decisions, perpetuating unnecessarily long delays and gaps in effective and timely safety communications and recall management, hindering the timely development of new and innovative treatment options, and increasing the overall costs and inefficiency of the healthcare system.
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.

In considering the role artificial intelligence can play in both the near and long-term future of outcomes centricity, we need to discuss and internalize the concept of Design Thinking which requires intense cross examination of the filters used in defining a problem and to revise the potential opportunities before developing strategies and tactics. Design Thinking requires cross-functional insights into a problem by varied perspectives as well as constant and relentless questioning. In Design Thinking observation takes center stage. In the "Sciences of the Artificial,” Herbert Simon has defined "design thinking" as the "transformation of existing conditions into preferred ones."

Unlike Critical Thinking, which is a process of analysis, Design Thinking is a creative process based around the creation of action-oriented ideas.

Artificial intelligence can be a revolutionary tool to develop those action-oriented ideas? And, just for the record, “action-oriented” and “pharmacovigilance” are not mutually exclusive terms.

Consider ISOP’S Special Interest Group, created in 2015 with the goal of designing novel risk minimization methods applied in a risk proportionate manner to specific populations.

In keeping with the theoretical underpinnings of Design Thinking and the practical applications of Artificial Intelligence, this initiative, (also referred to as the Post-Approval Vigilance Program), can more fully and swiftly develop a customizable decision aid yielding multiple levels of stringency to risk minimization interventions, leading to a more efficient, practical, and transparent planning of risk minimization activities.

To quote JM Eisenberg, the former Director of the US Agency for Healthcare Research and Quality, “Globalize the evidence, localize the decision.”

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 healthcare based on the needs and habits of patients, and provide regulators not just with more data, but better data in context.

We have not yet reached the state of “real” AI, but it is ready to sneak into our lives without any great announcement or fanfares – narrow AI is already in our cars, in Google searches, Amazon suggestions and in many other devices. Apple’s Siri, Microsoft’s Cortana, Google's OK Google, and Amazon’s Echo services extract
questions from speech using natural-language processing and then do a limited set of useful things, such as look for a restaurant, get driving directions, find an open slot for a meeting, or run a simple web search.

But can AI usage for adverse event reporting and prediction be far behind?

Here’s a more worrisome question: Do regulatory agencies have the IT, AI, and human resources chops to suss out the wheat from the chaff? As Dr. Donald Therasse (former VP of Global Patient Safety and Global Medical Affairs at Eli Lilly & Co.) commented at a recent conference, “The fear is not that we will find new information; it’s that we would overwhelm our current systems and capacity with poor quality information.” These worries beg the question of what staffing levels and training is required to adequately and appropriately handle the 21st century demands for pharmacovigilance data that is usable at a regulatory level.

If you’re wondering how global PV professionals from Washington to Delhi will address exponentially increasing amounts of Individual Case Safety Reports (ICSRs), sit back in your seats and consider that artificial intelligence will not only operate ICSR processing but also assist in their evaluation – including the direct collection of ICSRs from mobile devices.

Artificial intelligence is already found in several areas in healthcare, from data mining electronic health records to helping design treatment plans, from health assistance to medication management.

Artificial intelligence will have a huge impact on genetics and 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 DNA is altered by genetic variation, whether natural or therapeutic. Imagine the predictive capabilities for pharmacovigilance.

But making knowledge actionable requires the application of proven analytical methods and techniques in order to produce reliable conclusions. Until recently, such analysis was done by experts operating in centers that typically restricted access to data. This “walled garden” approach evolved for several reasons: the imperative to protect the privacy and confidentiality of sensitive medical data; concerns about the negative consequences that could arise from inappropriate, biased, or incompetent analysis; and, the tendency to see data as a competitive asset.

Regardless of the specific reason, the result has been the same: widespread and systemic barriers to data sharing.

If we are to reverse these tendencies and foster a new approach to creating evidence, we must bear in mind that there must be a common approach to how data is presented, reported and analyzed and strict methods for ensuring patient privacy and data security.
Rules of engagement must be transparent and developed through a process that builds consensus across borders and relevant ecosystem stakeholders. To ensure support across a diverse ecosystem that often includes competing priorities and incentives, outputs must be intended for the public good and be readily accessible to all stakeholders at the push of a button.

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.

What about the most popular current usage of artificial intelligence, mobile apps? According to a new research study fielded between December 2013 and January 2014, 72% of all US adult Rx patients are using mobile applications. That’s reality.

A national survey of 2,216 US patients (age 18+ who take at least one prescription medication per day) show that whether you’re a Millennial or a member of the Greatest Generation, you’re using apps via a smart phone or a tablet.

According to Robert Jamison, PhD, professor of anesthesia and psychiatry at Harvard Medical School and pain psychologist with Brigham and Women’s Hospital, mobile medicine is helping chronic pain patients cope with and manage their condition thanks to new smartphone apps, which can track patients from a distance and monitor pain, mood, physical activity, drug side effects, and treatment compliance.

And according to a new report just issued by the Center for Technology and Aging, medical optimization (“med-ops”) via information technology is an important element to improving medication-related errors and improving medication adherence among older adults. The report says “widespread use” of technology aimed at this population could save thousands of lives and billions of dollars.”

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

Will our socio-economic “technology gap” lead to a more pronounced pharmacovigilance gap?” It’s an important question. That’s why it’s crucial we remember there is no one-size-fits-all solution. Let’s face it, when it comes to mobile phones, any gap is rather narrow.

But we have to think beyond apps and the role of artificial intelligence has to be front and center.

As the American industrialist Walter O’Malley once opined, ”The future is just one damned thing after another.” Much depends not just on infrastructure, but also on capabilities, and trust.
The end goal is the same for all stakeholders -- ensuring optimal use of resources for healthcare systems; improving access to value-adding medicines for patients; and appropriate reward for innovation. But a key question we must ask ourselves is -- will we control the data, or will the data control us?

As management guru W. Edwards Deming once quipped,

“Change is not required. Survival is not necessary.”

Artificial Intelligence is here. Ladies and Gentlemen, fasten your seatbelts.