Proactive Pharmacovigilance: A New Model for the 21st Century

The discipline of pharmacovigilance (PV) largely originated in reaction to public health disasters caused by medications, e.g. tetanus toxoid (1912), sulfanilamide (1938), thalidomide (1962), etc. Approaches for detecting significant, previously unrecognised hazards of medications after their introduction into clinical use has been principally based on collecting anecdotal reports of suspected adverse drug reactions (ADRs). Further, communicating these new signals to regulators individually and/or in the aggregate within the required time frames has been driven by categories defined by degrees of clinical concern. Similarly, regulatory oversight of pharmaceutical company safety activities for their approved products was, until very recently, largely limited to assessing the adequacy of and compliance with the procedures licence-holders established to meet their legal obligations, rather than on any identifiable public health outcome. This movement from reactive, procedural based safety oversight to a practical, health based approach has been met with greater public awareness of drug safety issues. In addition, emerging informatics-based methods for acquiring and analysing medical information have sparked multiple global initiatives to research ways by which the present reactive system can be transformed into one that is proactive, robust, and more useful clinically.

Pharmacovigilance in the second decade of the 21st century is therefore in significant transition. Improving both the quality of data sources and the tools that are used to analyse the data is key to unleashing this new model. Modern information technologies such as data mining tools have evolved significantly and allow for enhanced identification of rare, medically important, ADRs. However, detection of meaningful drug-event associations, and drug interactions in particular, cannot be significantly improved simply by applying increasingly sophisticated analytical tools to data that is known to be inadequate and flawed. This becomes especially difficult, and may even be impossible, when a drug-related event is also relatively common in the untreated population, e.g. cardiovascular events in patients treated with NSAIDs, where an increased risk was eventually discovered in a large comparative clinical trial after going undetected by spontaneous reporting during decades of widespread global NSAID use. Since conducting such large trials is not feasible for more than a handful of drugs, post-approval PV will remain the mainstay for detecting new hazards of drugs after initial marketing approval based on the limited, essentially provisional, benefit-risk assessment obtained during clinical development. A major focus of new global PV initiatives is therefore the identification and/or creation of complete, clinically validated datasets to which more advanced analytical tools can be effectively applied.

Why do we Need a New PV Model?
PV needs to change from being reactive to regulatory compliance concerns that are conducted by an often isolated “safety” function within pharma companies to one that is more closely aligned with actual public health promotion. For medicines to be valued as important public health interventions, all of their users (prescribers, patients, caregivers) require clear understanding of their attributable benefits and harms, without which individual prescribers and patients cannot make informed, rational decisions on what benefits and risks are acceptable. PV must become a means of evaluating, understanding, and effectively communicating both the real-world benefits and risks for each patient-drug combination, and not merely a mechanism for identifying and quantifying overall population risks. During the next few decades, multiple avenues of research (e.g. genomics, epigenetics, metabolomics, microbiomics) will greatly increase our scientific understanding and identify many currently unknown factors that significantly affect individual patient responses, both positive and negative, to therapeutic agents. Biological and technological advances will improve understanding of disease mechanisms and individual patient response factors, and provide tools for better clinical decision-making and therapeutic choices, particularly the comparative benefits and risks of different interventions. PV should be in the forefront of making this explosion of knowledge accessible and comprehensible to every stakeholder in the therapeutic chain.

What Might Effective PV Look Like in 2038?
As stated above, scientific advances in biotherapeutics will create a shift away from our historical pharmaceutical model of “one size fits all”, with relatively minor modifications for relatively broad patient sub populations, e.g. the elderly, renally-impaired, etc., and towards individualisation of therapy. “Personalised medicine” will identify patients’ biological and disease characteristics and use them to tailor specific therapies for an individually optimised benefit-risk balance. Current PV methodology, which relies substantially on the analysis of large datasets of patients treated with palliative drugs for prolonged durations, does not support this model of therapeutic decision-making. New models will be needed for effective safety evaluation of novel therapies (stem cell transplants, gene therapy, live biotherapeutics, etc.), many of which may involve single or short-duration highly targeted treatments of small numbers of carefully selected patients.
patients in whom adverse effects may be delayed for very long periods. In this setting, effective therapeutic interventions will require highly accurate, reliable, and comprehensible information on benefits and risks.

“When you can measure what you are speaking about, and express it in numbers, you know something about it; but when you cannot express it in numbers, your knowledge is of a meagre and unsatisfactory kind” (Lord Kelvin). One challenge for PV will lie in developing tools for accurate qualitative and quantitative assessment of both benefits and risks from data that may differ greatly from that presently available.

**Availability of New Data Sources**

Regulatory agencies have been at the forefront of using electronic health record data and developing data-mining and analytical tools for active surveillance of real-world clinical information to supplement or supplant today’s largely anecdotal safety data. The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) comprises over 170 research centres and healthcare data providers, with a comprehensive, searchable database and a registry of data sources for post-authorisation studies. In the USA, the FDA and the National Institutes of Health established the Observational Medical Outcomes Partnership to research analytical methods for systematic, proactive, and cost-effective use of electronic medical databases. The FDA also created the mini-Sentinel system for active surveillance, which links multiple healthcare data sources; this system contained >130 million individual patient records as of Dec 2012. Additional FDA safety initiatives include a pilot of pharmacological mechanism-based safety prediction and development of data-mining software for safety signal detection in literature reports that can “efficiently distinguish real signals from background noise in huge pharmacovigilance databases.” Finally, new safety signals may be identified or communicated via the web, social media, “cloud” storage etc. Early examples include analysis of web searches to identify epidemiological trends in influenza and data-mining of free-text clinical notes for hypothesis generation and analysis of suspected ADRs.

There are multiple commercial developers and providers of various types of software for analysis of clinical “big data”. However, these disparate data sources require new methods and analytical tools, including standardisation of benefit and risk characterisation, terminologies, data structures, outcome definitions, comparator selection, signal triage, privacy protection, etc., which are currently at a very preliminary, exploratory stage. Once validated, such standards and tools should allow more accurate determination of drug benefits and risks in actual clinical practice compared with the limited information derived from controlled trials. Multivariate analysis will identify patient subpopulations in whom the benefit-risk balance is optimal or unfavourable, permitting assessment of true clinical practice effectiveness, as opposed to the “two adequate well-controlled trials” required to prove statistical efficacy in a small, relatively homogeneous patient population. Additionally, these analyses should permit comparison of the benefit-risk balance for multiple treatment options in actual clinical usage, which is almost completely lacking today. Current labelling regulations do not permit updating of efficacy information without new controlled studies and might require significant changes to accommodate these new types of analyses.

**Better Clinical Decision-making**

Marketers and regulators of therapeutic products are obligated to ensure that reliable, actionable clinical information is effectively communicated to prescribers and users to allow informed therapeutic choices based on balancing benefits and risks. However, the ever-increasing flood of medical information far exceeds individual human capacity to assimilate and apply it. Today’s passive dissemination of information is already inadequate for patient protection – it lacks sophisticated decision support systems to match and evaluate patient-specific factors and drug characteristics to ensure appropriate medication choice and administration. It is also insufficient for this information to be available and comprehensible only to healthcare providers; patients and caregivers require access to the relevant information in an intelligible and actionable format.

Greater understanding of the drivers of prescriber and patient behaviour and factors that influence them is necessary for successful interventions to improve the understanding of benefits and risks. This will require research into the sociological and psychological bases of such decision-making. In the USA today, healthcare activity is largely reactive and driven by financial incentives towards interventions, rather than prophylaxis. To change this paradigm, healthcare delivery requires incentives for data-driven risk prevention. Patients and caregivers will need to be active, health-literate participants in both regulatory and individual decisions regarding acceptable medication use.

**Broad Accessibility of Appropriate Information**

Open access to benefit-risk information for both investigational and marketed drugs is steadily increasing. Spontaneously reported adverse event data from the FDA safety database has been publicly available for many years, although not in a readily accessible or usable format, while comparable data...
Information about ongoing activities such as unconfirmed safety signals undergoing evaluation. These actions are intended to improve clinical decision-making and enhance public confidence in the system by making source data and benefit-risk assessments available and transparent. However, this is predicated on users’ initiatives to make summary and even raw study data available appropriately.

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Cost-benefit Considerations
Drug development costs have been increasing steadily for many years, while the pipeline of new products continues to shrink. While the business model in which giant global companies develop a few highly profitable “blockbuster” products that are taken long-term by millions will become less prevalent, it is reasonable to assume that multiple smaller companies with particular biotechnology research expertise will emerge to develop specialised therapies for much smaller numbers of selected patients. These companies will generally not have the in-house expertise to navigate the current global regulatory maze, and will almost certainly have to obtain support from appropriate external providers or partners. If these trends do emerge, it will become more difficult, and there will be fewer opportunities, to recoup expenses and generate profits, so new models of drug development and reimbursement will be needed. Engagement of all stakeholders - patients, healthcare providers, payers, regulators, and industry – will be needed to minimise resource limitations and unnecessary costs.

Demographic changes, including global population growth, increased prevalence of disorders associated with Western lifestyles, emerging infectious diseases, and the increasing proportion of elderly people who are both more susceptible to ADRs and use more medications, will also alter perspectives on cost-benefit-risk.

Future PV activities will require demonstrable cost-effective public benefit, and regulatory trends towards bureaucratisation and disharmonisation be reversed.

Conclusion
The impact of 21st century technologies on healthcare delivery will create significant challenges and opportunities for all stakeholders in pharmaceuticals. PV is currently in transition, with new sources of medical information and methods for its analysis being explored to transform the current reactive system into proactive benefit-risk management fully adapted to modern technology and needs. Regulations are gradually evolving towards a more proactive approach, but remain too procedurally focused, often inhibiting innovation, while the technical resources required for effective benefit-risk assessment are still at an early development stage. In summary, PV is entering uncharted territory requiring industry, regulators, healthcare providers, and patients to confront multiple unknowns that will eventually lead to enhanced benefit-risk assessment, communication and implementation.

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