

# Proactive Pharmacovigilance

## A New Model for the 21st Century

Twenty-first century technologies will create significant opportunities and challenges for all healthcare stakeholders. Pharmacovigilance (PV) too is in transition, with new sources of medical information and methods for its analysis that will transform today's largely reactive system into proactive benefit-risk management for all medication users.

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The discipline of PV largely originated in reaction to public health disasters caused by medications, e.g., tetanus toxoid (1912), sulfanilamide (1938), thalidomide (1962). The detection of significant, previously unrecognized hazards of medications following their introduction into clinical use was traditionally based on collation and evaluation of essentially anecdotal reports of suspected adverse drug reactions (ADRs).

Subsets of these reports were communicated to regulators, individually and/or in the aggregate, within specific timeframes; however, these regulations were established at a time when modern communication tools and databases did not exist and all communication was on paper, greatly limiting the analysis and evaluation of potential safety signals.

Furthermore, regulatory oversight of company safety activities for approved medical products was, until very recently, largely limited to assessing the adequacy of and compliance with the procedures license holders established to meet their legal obligations, rather than on any identifiable public health benefit.

In recent years, the combination of greater public awareness of drug safety issues and emerging informatics-based methods for acquiring and analyzing medical information has sparked global research initiatives for transforming the present, largely reactive system into one that is proactive, robust and more useful clinically.

While technologies such as data mining may permit reader identification of rare, medically important ADRs, the detection of clinically important drug-associated events and drug interactions cannot be significantly improved simply by applying increasingly sophisticated analytical tools to ever-increasing volumes of anecdotal data that remains inadequate and flawed. PV is therefore undergoing a major transition in which improving both the quality of data sources and the tools used for data analysis is pivotal.

Post-approval PV will continue to be the mainstay for detecting previously unidentified harms due to drugs after their licensing based on the provisional benefit-risk assessment identified during development. However, one especially challenging scenario is the detection of a drug-related increase in the incidence of an event that is relatively common in the unexposed population – a classical “signal-to-noise” problem. For example, the increased risk of cardiovascular events associated with nonsteroidal anti-inflammatory drugs (NSAIDs) was discovered only in a large comparative clinical trial of a newer drug, having gone undetected by traditional PV methods during decades of widespread NSAID use.

Similarly, provisional evidence sufficiently convincing for regulatory action, e.g., the supposed increase in cardiovascular risk attributed to rosiglitazone, may prove unfounded by subsequent studies.

Since it is not feasible to conduct large prospective trials for more than a very small number of drugs, a principal focus of new PV initiatives is the identification and/or creation of complete, validated data sets reflecting real-world clinical use that can be analyzed to assess the true risks of a drug in very large numbers of patients.

## Why Do We Need a New PV Model?

PV needs to be refocused as a function closely aligned with actual public health benefit rather than its historical primary focus on regulatory compliance concerns conducted by an often isolated “safety” function within life science companies.

For medicines to be properly appreciated as important public health interventions, all their users, especially patients, require a clear understanding of their attributable benefits and harms. Without that understanding, individual prescribers and patients cannot make informed decisions on what benefits and risks are acceptable. PV must therefore 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 approximately quantifying overall population risks. In the near future advances in genomics, epigenetics, metabolomics, microbiomics etc., will transform our understanding of disease mechanisms and individual patient response factors, both positive and negative, to therapeutic agents. This will provide new qualitative and quantitative tools for clinical decision making and therapeutic choices, especially 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 20 or 25 Years?

Scientific advances in biotherapeutics will create a shift toward individualization of therapy and away from our historical model of “one size fits all”, with relatively minor modifications for relatively broad patient sub-populations, e.g., the elderly, renally impaired, etc. “Personalized medicine” will use patients’ specific biological and disease characteristics to tailor therapies for an individually optimized benefit-risk balance.

Current PV relies largely on the analysis of relatively large numbers of poorly defined individual patients taking palliative drugs for prolonged durations, and does not support an individualized model of therapeutic decision making. New models will be needed for effective safety evaluation of novel therapies (stem cell transplants, gene therapy, live biotherapeutics), many of which may involve single or shortduration, narrowly targeted treatments of small numbers of highly selected patients in whom adverse effects may be delayed for very long periods. In this setting, effective therapeutic interventions will require 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 meager and unsatisfactory kind” (Lord Kelvin). One major challenge for PV will be to develop tools for accurate qualitative and quantitative assessment of both benefits and risks using data that will differ greatly from that used historically.

## New Data Sources

Regulatory agencies have been at the forefront of using electronic health record data and developing signaling 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 centers and healthcare data providers, with a comprehensive, searchable database and a registry of data sources for post-authorization studies. In the U.S., the FDA and the National Institutes of Health established the Observational Medical Outcomes Partnership to research analytical methods for the 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 December 2012. 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 influenza epidemiological trends and data mining of free-text clinical notes for hypothesis generation and analysis of suspected ADRs.

There are several commercial developers and providers of various types of software for analysis of clinical “big data”. The multiplicity of disparate data sources requires new methods, analytical tools and standardization of attributes including benefit and risk outcomes, terminologies, data structures, signal triage, privacy protection, etc., which are presently 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 than the limited information derived from controlled trials. Multivariate analysis will identify patient sub-populations in whom the benefit-risk balance is optimal or unfavorable, permitting assessment of true clinical practice effectiveness, as opposed to today’s “two adequate well-controlled trials” required to prove statistical efficacy in a limited patient population. Additionally, these analyses should permit actual clinical usage comparison of the benefit-risk balance for multiple treatment options, which is now almost completely lacking.

## Better Clinical Decision Making

Marketers, regulators and dispensers 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.

The ever-increasing flood of medical information far exceeds individual human capacity to assimilate and apply it. Passive dissemination of minimally structured information, such as text-based prescribing information, is insufficient to provide robust patient protection; rather, sophisticated decision support systems, which are presently at a very early developmental stage, are needed to help prescribers choose appropriate medications based on patient and drug-specific characteristics. It is also insufficient for such information to be available and comprehensible only to healthcare providers; patients and caregivers need ready access to relevant information in an intelligible and actionable format.

Greater understanding of the drivers of prescriber and patient behavior 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, the development of incentives and methods for data-driven risk prevention and reorientation toward prophylaxis of today's reactive, illness-focused, intervention-driven medical systems. 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 (AE) 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 from the EU is now directly accessible via the web. FDA and EU public websites list ongoing clinical trials. The FDA posts the most frequently occurring clinical trial AEs. There are initiatives to make summary and even raw study data available appropriately. EU Pharmacovigilance Risk Assessment Committee deliberations are posted on the web, while the FDA publishes 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 the users' ability to evaluate both benefits and risks accurately, and the impact, if any, of this level of transparency on actual health outcomes remains to be determined.

## Cost-Benefit Considerations

Future PV activities will require demonstrable cost-effective public health benefits, and regulatory trends toward bureaucratization and global disharmonization must be reversed.

Drug development costs have been increasing steadily for many years, while the pipeline of new products continues to shrink despite increasing clinical need, e.g., for infectious diseases and degenerative disorders in an increasingly elderly population. The business model in which giant global companies develop small numbers of highly profitable "blockbuster" products taken long-term by millions of patients for disease palliation, rather than cure, will become less common. It is reasonable to assume that multiple smaller companies with specifically focused research expertise will emerge to develop specialized therapies for much smaller numbers of highly selected patients. Such companies will generally not have the in-house expertise to navigate the global regulatory maze, and will almost certainly need support from external providers or partners with that expertise. The trends will create greater difficulty and fewer opportunities to recoup expenses and generate profits, which will in turn require new models of drug development and reimbursement. All stakeholders – patients, healthcare providers, payers, regulators and pharmaceutical companies – will need to be fully engaged to lower resource limitations and eliminate 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 need to demonstrate cost-effective public health benefits, and, recent regulatory trends toward increased bureaucratization and reduced global disharmonization must be reversed as quickly as possible.

## Conclusion

The impact of 21st century technologies on healthcare delivery will create significant challenges and opportunities for all stakeholders in life sciences. PV is currently in transition, with new sources of medical information and methods for its analysis being explored that will transform the current reactive system into proactive benefit-risk management using emerging medical information technology. Regulations are gradually evolving toward 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 a nearly developmental stage. In summary, PV is entering uncharted territory requiring industry, regulators, healthcare providers and patients to address multiple unknowns and should eventually lead to greatly enhanced benefit-risk assessment, communication and implementation.

## References

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