The New Post-marketing Pharmacovigilance Toolbox

Peter K Honig, MD, MPH



Peter Honig, MD, MPH, is currently Head of Global Regulatory Affairs at AstraZeneca. Dr Honig received his baccalaureate, medical, and public health degrees from Columbia University in New York. He has postgraduate training and is board-certified in internal medicine and clinical pharmacology, and has authored numerous peer-reviewed publications and book chapters. He has held senior leadership positions at the US Food and Drug Administration and Merck Research Laboratories. He has been the PhRMA representative at the International Conference on Harmonization (ICH) Steering Committee since 2002 and is the current co-chair of the ICH Global Cooperation Group, whose mission is to promote regulatory harmonization in non-ICH countries and regions. Dr Honig has a faculty appointment at the Uniformed Services University of the Health Sciences and is an Associate Editor of *Nature Clinical Pharmacology and Therapeutics*.

Like the pharmaceutical industry, pharmacovigilance is entering a period of transition. The past 10 years have seen several new developments in pharmaceutical legislation, all aimed at improving safety, and have placed pharmacovigilance on the critical path for the approval of new medicinal products. This pathway has seen the development of new methodologies that aim to reduce residual uncertainty prior to approval. The hope is that, in populating a pharmacovigilance toolbox with new scientific and technical methods, safety assessment and surveillance of medicines can be conducted in a very structured way and appreciation for residual uncertainty will become the norm. As the regulatory landscape continues to evolve, it is vital that regulators and drug manufacturers alike embrace regulatory science and the use of risk management tools.

Pharmacovigilance does not begin with drug approval. It begins with the informed activities of drug discovery. Good pharmacovigilance requires:

- a prepared mind that is trained and experienced in disease biology;
- an intimate knowledge of the drug and its pharmacology;
- knowledge of the sources of variability in drug absorption, distribution, metabolism, and excretion (ADME);
- the effects of disease, comorbidities, and extrinsic environmental factors on efficacy and safety; and
- how the drug is to be used in the marketplace.

Furthermore, it is recognized that pharmacovigilance also requires knowledge of the disease states in which the drug will be used, and the background rates of potential and untoward outcomes. Untoward outcomes may be limited or even eliminated by good standardization of processes and knowledge management.

The past 10 years have seen several new developments in pharmaceutical legislation and regulation in Europe and the US, all aimed at improving safety. Current regulatory frameworks, as a result of changes in legislation and guidelines, have placed pharmacovigilance on the critical path for the approval of new medicinal products.

Pharmacovigilance in the US

From a US perspective, understanding current regulatory frameworks and new developments requires an additional knowledge of healthcare systems. The US healthcare system's undoubted ability to manage risk is second only to practitioners who understand the strengths and limitations of clinical trials and observational data and when to apply them. The Federal Food, Drug, and Cosmetic Act, as amended in 1962, discusses 'safe' and 'effective' as absolute concepts. When any drug is launched onto the market there is residual uncertainty—with an ultimate benefit and an ultimate risk involved. Risk tolerance is contextual to disease severity. Patients with life-threatening diseases are willing to tolerate a greater degree of risk than those that have a stuffy nose and are taking antihistamines.

The political and regulatory environment in the US has evolved considerably since those early years. The latest passage by Congress of the Food and Drug Administration Amendments Act (FDAAA), on September 27, 2007, provides the US Food and Drug Administration (FDA) with sweeping new regulatory authority over investigational and marketed drugs.[1]

The FDAAA also provides a new legal framework for integrating risk evaluation and minimization strategies (REMS) into medical product reviews and post-marketing activities. REMS include, but are not limited to, mandatory medication guides for patients, restricted distribution systems for designated therapeutics, and assessment of the effectiveness of such programs in minimizing product risks. This requires pharmaceutical companies to take increasing responsibility for managing risks in the marketplace. Regulators are also requiring more structured assessment of post-marketing experience through registries, development safety update reports (DSURs), and formal pharmaco-epidemiology assessments. One must remember that the FDA's new legal authority impacts not only the regulated

1. US Food and Drug Administration, HR 3580: The Food and Drug Administration Amendments Act, 2007. Available at: www.fda.gov/oc/initiatives/hr3580.pdf
2. Burkhart GA, Sevka MJ, Temple RJ, Honig PK, Temporal decline in filling prescriptions for terfenadine closely in time with those for either ketoconazole or erythromycin, Clin Pharmacol Ther 1997;61:93–6.
3. Graham DJ, Drinkard CR, Shaitin D, et al., Liver enzyme monitoring in patients treated with troglitazone, *JAMA*, 2001;286:831–3.
4. Jones JK, Fife D, Curkendall S, Goehring E Jr, et al., Coprescribing and codispensing of cisapride and contraindicated drugs, *JAMA*, 2001;286:1607–9.

© TOUCH BRIEFINGS 2011

pharmaceutical industry but also prescribers and patients through the adoption and use of REMS, as well as the timing of approvals and accessibility of new medicines. The FDA's perspectives are also informed by experiences with terfenadine, cisapride, and troglitazone, which catalyzed introspection on the effectiveness of managing the known risks of medicines.[2-4]

International Legislation

In Europe, new legislation requires companies to collect, collate, and evaluate information about suspected adverse reactions. The EU now requires companies to submit periodic safety update reports (PSURs), which are intended to provide updates of the worldwide safety experience of a product. The reports have to be filed every six months for the first two years that a drug is on the market and once a year thereafter.

The US Congress and worldwide regulators, as well as the drug-development industry, are considering how to best address many of the components of this. As they do so, they must remember that benefit:risk assessment requires a balanced approach that, at the end of the day, takes into consideration the needs and interests of patients and the exigencies of current healthcare delivery infrastructures. This is a complicated systems-based opportunity that deserves thoughtful solutions.

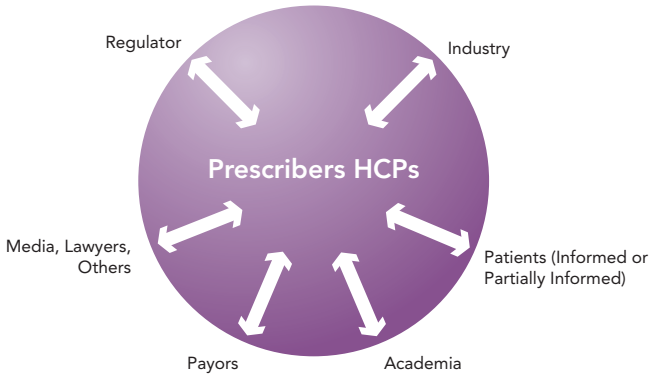
The Healthcare Environment Equilibrium

Current regulatory arrangements work effectively to provide a culture of medicine safety and confidence within the authorities and the medical industry. By developing lines of good communication between all interested parties, they are best able to function efficiently and ethically, particularly in times of crisis (see *Figure 1*).

Some argue this is not enough. To be more effective, drug regulatory authorities need to extend their reach further. Good communication certainly extends toward the public perception of a given medicine. It is not sufficient, however, for the experts to be satisfied with a medicine's safety profile. Critical questions that medicine providers need to consider when communicating with patients and the general public include: 'how safe is safe enough?' and 'which risks are acceptable?' These questions take on a greater significance when one considers the dramatic erosion of trust between interested parties, exacerbated by prior experiences, drug safety crises, and drug safety withdrawals. One points to an abandonment of the first principle of fidelity to patient interests and the need for available information to be brought to the fore. Communication is not just about availability of information, especially in the area of risk where the complexity can be overwhelming. The science of appropriate risk communication must be applied to help patients make informed decisions about complex issues in their treatments.

Formulating a better risk-communication strategy starts long before the regulatory process even begins. For a pharmacovigilance system to work, pharmaceutical companies must integrate risk-management systems and effectively change the company culture that equates risk with failure. Effective risk communication, which essentially sets the perception of product risk, is fast becoming the single most important consideration in risk-management strategies.

Figure 1: The Healthcare Environment Equilibrium



HCP = healthcare professional.

Promoting a successful safety culture and risk-communication strategy requires companies to integrate safety risk management within the context of their overall business strategies. This demands not only medical, scientific, and regulatory expertise but also first-class technology expertise to drive premium and efficient processes, establish governance, and measure results. It also requires better communication with all stakeholders, including patients, doctors, regulators, and advocacy groups.

One should not rely on a single tool but rather a set of tools that bring together structured methodologies. These should include data mining of large data sets from several sources, individual case reviews and assessments, and, finally, independent validation of those findings. The validated findings must be communicated in terms that can be understood by each audience: regulators, the pharmaceutical industry, the financial community, healthcare providers and payors, prescribers, and patients.

An important issue relates to the US statutory requirement for a drug to be cleared for (or remain on) the market: that it is "safe and effective… when used in accordance with proposed labeling".[5] The reality, however, is that 'safe and effective' as an absolute concept is difficult to define. Except in specific cases, patient awareness and acceptance of risk are low. Moreover, there is little real confidence in physician- and patient-directed labeling to manage risk. Physicians have decreased capability in risk numeracy, pharmacology, and integrating evidence into practice. Unfortunately, physicians are not systematically trained in these aspects. Furthermore, while spontaneous reporting has demonstrated value in detecting adverse experiences that rarely occur as background in the target population (e.g. drug-induced liver injury, *torsades de pointes*, etc.), it has very little value or reliability in detecting, much less quantifying, increased rates of more-common adverse reactions.

The Value of Data and Need for Transparency

Regulatory assessment of an acceptable benefit:risk balance remains a matter of considerable public attention. Increased scrutiny means regulators are provided with significantly more data on investigational medical products than in the past. In principle, regulators are looking to reduce residual uncertainty prior to approval and benefit:risk must be interpreted in the context of the nature and severity of the disease

5. US Food and Drug Administration, Code of Federal Regulations, Title 21, Volume 5, Revised as of April 1, 2010, CITE: 21CFR314. Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?cfrpart=314&showfr=1&subpartnode=21:5.0.1.1.4.9

and the countervailing key risks of the medicinal product. Structured approaches could be beneficial in enhancing consistency, predictability, and transparency, and this has been recognized by some regulatory authorities.[6]

One of the FDAAA titles details one of the more significant changes and requires that controlled clinical investigations (except for Phase I clinical investigations) for investigational or marketed products are registered on the National Library of Medicine (NLM) website (www.clinicaltrials.gov). It also requires the establishment of an NLM results database for registered trials and provides a timeframe for public disclosure of the trial results with the allowance for significant civil monetary penalties. These provisions are a direct response to the public call for increased transparency of clinical research. Certainly, it is a fine juggling act for regulatory authorities as they now need to balance transparency of data and decision-making with risks to public confidence with third-party analyses of publicly available data and the timeliness of regulatory decisions.

Many critics argue that we have entered an era of increasingly frequent publication of meta-analyses, some of which identify potential safety signals. Such publications commonly lead to urgent calls to take immediate regulatory action, without acknowledgment of potential pitfalls in the interpretation of data. The continuing evaluation of potential safety signals at the FDA requires assessment of all available data from many sources.[6] However, there is no standard agreement of what an early signal is. Consequently, this creates a problem because the FDA, healthcare providers, and pharmaceutical companies all need to have a common understanding and agreement of what an early signal is that then allows each associated stakeholder to take the appropriate action.

The FDA's efforts to increase communication of new safety information and the mandated increased transparency of new medical product information aim to address a data transparency issue that could arise as the result of a lack of a standardized approach or rules of conduct. With no universal approach, data access becomes a threat and many data owners will realize that what they own becomes a commodity with enormous value. Improved access to data from multiple sources supports the early detection of safety issues to avoid undue risk for patients. Not to have access to these data will impede the continuing evolution of good pharmacovigilance.

Breaking Down Organizational Silos as a Risk Communication Strategy

Breaking down organizational silos with technology to foster better risk communication strategies has become one of the biggest challenges in tracking adverse events during clinical trials.

A major factor is the way that pharmaceutical companies traditionally operate silos of information independently of one another. Trial data are typically gathered by multiple systems that are not fully integrated, so essential data cannot easily be tracked or transferred between systems. As a result, some trial data must be entered multiple times in separate systems, which reduces data quality, increases costs, and impedes strategic data analysis. This results in duplicated efforts among various clinical groups, a lack of collaboration, and a failure to put in place best practice clinical development processes.

Integrated data systems that work together can eliminate multiple points of data entry and support easier transfer of data. The right technology solution should allow users across the company to access, review, and analyze a common clinical database—even if the systems themselves are not fully integrated.

Nowadays, a risk management suite of products should include signal detection and management capabilities, advanced analytics, and *ad hoc* reporting capabilities that provide visibility into strategic data across the enterprise. The interoperable solutions should be able to unlock data that are traditionally held in silos.

Improving Predictive Models

In 2004 an FDA report concluded the agency needed a toolbox of new scientific and technical methods—animal or computer-based predictive models, biomarkers for safety and effectiveness, and new clinical evaluation techniques—to improve the predictability and efficiency of drugs along the critical path from laboratory to product.[7] Essentially, a toolbox to reduce residual uncertainty prior to approval.

That was six years ago, yet the applied sciences used in drug development are still lagging behind the swift progress of basic science, and existing preclinical models and paradigms often fail to predict toxicology that emerges later in development.

The consequences of the FDA's need to reduce residual uncertainty during the preapproval period are: larger clinical safety databases; broader assessments of 'vulnerable' populations and risk capping for specific risks, for example cardiovascular risk with oral hypoglycemics; and specific prospective assessment of risks, for example structured mood and suicidality adjudication for many/most centrally acting drugs. These are data that can be fed back into predictive models.

In order to ease the bottleneck of drug development that stifles medical progress, the critical path must look to alternative methods to accelerate a drug's progress. Techniques such as *in silico* modeling, simulation, and using quantitative disease models are frequently cited as the next step in creating more informative and predictive development designs. These strategies are underpinned by the science and principles of clinical pharmacology.[8]

Some well-known models exist and they fall into three general categories: (i) models applied to individual clinical trial results that are applied to populations or individual patients; (ii) models for specific classes of drugs; and (iii) generalized models. One well-known model based on clinical trial data includes the familiar mathematical models based on NNT (numbers needed to treat) and NNH (numbers needed to harm).[9]

6. Michele TM, Pinheiro S, Iyasu S, The safety of tiotropium—the FDA's conclusions, *N Engl J Med,* 2010;363:1097–9.
7. Kaplan W, Benefit, Risk and Innovation in Pharmaceutical Research and Development: Opportunities and Issues, 2004. Available at: http://archives.who.int/prioritymeds/report/background/barriers.doc
8. Honig P, Lalonde R, The economics of drug development: a grim reality and a role for clinical pharmacology, *Clin Pharmacol Ther,* 2010;87:247–51.
9. Honig P, Benefit and risk assessment in drug development and utilization: a role for clinical pharmacology, *Clin Pharmacol Ther,* 2007;82:109–12.

These are familiar concepts to most practitioners of evidence-based medicine; however, the application to drug benefit:risk assessment has significant problems because it is highly dependent on the background rates of disease severity and adverse events.

While modeling goes hand-in-hand with experimentation, it's hard to pick out the specific impact of modeling alone. However, the broad and continued application of models in the industry is a compelling argument for their value. In addition, the interest in combining different predictive methods to study more-complex and diverse systems is gaining momentum among researchers. Converging knowledge must occur if these models are to have any chance of success.

Tomorrow's predictive modeling must find new ways to combine information, including new and existing types of data. Moreover, predictive modeling needs ways to integrate different kinds of data, such as numbers from experiments and unstructured information, like text. For predictive computer modeling to enter the next evolutionary stage, solutions are needed that combine advanced simulation capabilities with enormous databases that are filled with information about patients, including their genotypes, disease state, and reaction to therapy. Even further along the line, potential side effects or unanticipated effects of drugs at the molecular level could be illustrated by techniques such as building and animating 3D protein models and watching them interact as a disease progresses, regresses, and reacts to therapies.

Improving models in early-stage development that incorporate advanced computer modeling will take more than just software. Stable chemistries suitable to automated mass production of varied, drug-like compounds would also be required. For the foreseeable future, compounds will still be tested in animals and humans. However, advances in science might develop fully formed organs for testing.

Developing Evolvable Systems and Adding New Processes

The reach of pharmacovigilance continues to extend as the range of medicinal products grows and there is a growing realization among regulators that safety is more than monitoring, detection, and assessment of adverse drug reactions (ADRs) occurring under clearly defined conditions and within a specific dose range.

Current thinking suggests that systems need to evolve in order to address a broad pattern of drug use within society. Increasing use of traditional and herbal medicines in combination with other medicines, illegal sale of medicines and drugs of abuse over the Internet increasing self medication practices, medication errors, and lack of efficacy are all within the domain of pharmacovigilance.

As systems adapt to the demands of pharmacovigilance, the signs point to technological advances that enable new processes to be added that aid in the risk management process. One such example has seen healthcare systems switch over to electronic medical records as potential sources of data that could be utilized for research in safety and risk management. Because of the large number and detail of the variables, which can be combined to generate new diagnoses or adverse events, hypotheses can be explored that are not restricted to existing diagnoses.

Robust Signal Management Systems

Ultimately, more-robust systems for the more rapid accumulation of post-market information are required that encourage collaboration among providers, payers, and the pharmaceutical industry around issues of drug safety.

Better systems are also needed for detecting rare side effects sooner, for fully evaluating these signals, and for better vehicles that communicate this information to providers and patients so that people can make informed choices. This includes better systems for engaging in more-proactive, real-time surveillance for potential drug safety issues. We are now better able to detect those idiosyncratic safety issues—metabolism and transporter-based interactions, renal tubule damage—and we are improving in terms of detecting these signals in preclinical species and clinical studies. Once these signals are detected, the FDA needs better tools and resources for marshalling evaluations of the signals to discern if they're real.

Conclusion

The hope is that, in populating a toolbox so pharmacovigilance can be carried out in a very structured way, an appreciation for residual uncertainty becomes the norm, and a structured benefit:risk assessment provides tolerances. In this way, residual uncertainty can be identified and the strength of a decision to approve a drug or leave it on the market can realistically be evaluated.

The regulatory environment continues to have approved preclinical predictive models, and rules for analyses for interpreting publicly available data. By moving towards sentinel and robust safety measures regulators can be assured that safety issues will be picked up and quantified. Regulatory inspections continue to migrate to risk-based approaches that ensure there are no meaningless compliance checks on the timeliness of recording. The knock-on effect sees regulatory science emerge on the expectations and use of risk management tools.

Has the current drug development and approval paradigm outlived its usefulness? Commentators have concluded that the fully integrated pharmaceutical company that engages in the full spectrum of discovery, development, and marketing of new therapeutics is a model whose time has come—and gone.[10] Would we thus be better served by demonstrating efficacy in an enriched population, where an effectiveness and safety in a broader population prior to approval are both observed?

The criticism here is by using a highly enriched population there has always been a general relevance to the patients that will be using the drug in question. This would solve the problem and conditional approval would be granted along with a structured release into a system that has more of a robust safety net.

If an enriched population is used, there are some contingencies that would require revisiting patent and exclusivity laws; but whether this is a win-win situation is debatable. At the end of the day, could we have faster trial rules and development of these drugs, and better and more-relevant data with fewer surprises? I think we have to watch this space. ■

10. Kaitin KI, Deconstructing the drug development process: the new face of innovation, *Clin Pharmacol Ther*, 2010;87:356–61.