
POST-LICENSING SURVEILLANCE OF THE SAFETY AND EFFICACY OF NEW DRUGS, BIOLOGICS, AND DEVICES

*AN ACTION PLAN FOR THE DEVELOPMENT OF A NATIONAL
PHARMACOVIGILANCE SYSTEM*

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1. INTRODUCTION

On September 7, 2007, a forum and workshop session was held at the Hall of States, Washington, DC: “*Pharmacovigilance Forum: Defining the Action Plan.*” The Forum was made possible by the generous support of: Arthritis Foundation of National Capital Area (NCA), Bristol-Myers Squibb Company, EWyatt Consulting, Henry M. Jackson Foundation for the Advancement of Military Medicine, and Noblis.

The purpose of the forum was twofold: (1) to validate a perspective or understanding of the pharmacovigilance problem in our nation in an objective environment, with as many representative stakeholder groups as possible; and, (2) to propose a model or framework, through which the stakeholders could develop an action plan to address the myriad of pharmacovigilance issues, and identify the leadership to move towards a coordinated solution. See Appendix A for a list of the stakeholders participating in the forum, speakers, and the topics presented.

While there are many pharmacovigilance activities in progress, most are narrowly focused and may not include representatives of the key stakeholder groups. The Forum explored progress to date in addressing the recommendations of the previous IOM Panel on drug safety (published September 26, 2006),¹ and sought to define a continuing agenda for problem-solving over time. It is the view of Noblis that a Patient-Focused, systems approach will be critical to the success of a pharmacovigilance-based, Phase IV Trials enterprise that will provide timely and accessible data on efficacy and safety of new and currently available drugs, devices, and biologics and restore trust in the science of drug discovery.

The information presented in this paper is derived from a review of industry literature and the discussion held during the forum. Presented here is a description of the current state, considerations for future state solutions, and a call to action detailed in the approach for moving forward.

2. ACTION PLAN FOR PHARMACOVIGILANCE – A NATIONAL PRIORITY

2.1 Nature of the Problem

The trust of the average citizen in the safety of drugs, biologics, and devices has been seriously undermined by a series of recent events, including revelations regarding the cardiac toxicity of Vioxx®,² the malfunction of pacemakers and implantable defibrillators,³ and the near death of six normal volunteers in England, in whom a new biologic agent being tested for use in arthritis and other autoimmune diseases unleashed a flood of unintended and “unforeseen” events.⁴ It would seem that nearly every day the public is treated to news of a failure of the healthcare system to protect them from harm from a new or old drug, developed and marketed in good faith to improve the health and well-being of the approximately 100 million people in this country who depend upon prescription drugs.⁵ At the very same time (often in the same publications), alarms are raised about the failure of the system to provide adequate support for basic and clinical research (including funding for the training of new scientists)⁶ and the “drying up” of the pipeline of new drugs and devices to treat chronic diseases.⁷ A Harris poll published in May, 2006, demonstrated that a majority of the people surveyed (64%) did *not* think that the FDA “does a good or excellent job of ensuring drug safety”, increased from 44% in 2004.⁸ While the FDA and its Center for Drug Evaluation and Research (CDER) are at the forefront to ensure that safe and effective drugs are available to, and used safely by, the American public, our current pharmacovigilance system ‘at-large’ is an intricate web of independent and interdependent stakeholders contributing to the status of the situation.

When considering the situation of patients with serious illnesses, it is easy to appreciate that at least two, sometimes countervailing, forces are at work in the public domain informing this discussion. Too often the issues become lost in a polarized discussion, pitting the supporters of rapid implementation of new drugs and unfettered access (usually the afflicted patient community) against those who express primary concern regarding the safety of new drugs. The National Health Council (NHC) recently published data from a survey of patients with chronic diseases and/or disabilities, in which questions were asked regarding prescription drug safety, benefit, and risk.⁵ In this patient population, the responses were complex but overwhelmingly in

favor of full disclosure of risk information coupled with no limitations to access to medications found effective. The challenge will be how best to communicate adequate information on the risk/benefit equation to as many people as possible in language that is understandable and obtain “informed consent” to proceed – particularly in the face of limited knowledge, a situation which characterizes the new agent profile. At the same time, it will be critical to determine how best to adjudicate liability and mitigate risk during ongoing data collection in the post-approval or post-licensing period, recognizing that not all risks can possibly be known when a drug is approved for public distribution. While one critical focus must be on better surveillance systems and detection of safety signals, an equally important area for research and development is the mechanisms by which new drugs work, not always known at the time of their approval for marketing.

2.2 Current State

Drug, biologic, and device development focuses heavily on pre-clinical data (animal testing, etc.) and most particularly on the results of Phases I through III clinical trials. In Phase I trials, typically normal human subjects are studied to determine the clearance of the drug from the body (pharmacokinetics) and for signs of side effects, or toxicity. In Phase I studies of new cancer drugs, for example, patients with a variety of advanced cancers are evaluated for pharmacokinetics, drug toxicity, and possible efficacy in reducing tumor size. Phases II/III trials enroll patients with the relevant disease for dose-finding (i.e., escalating doses) - to determine the optimal range of a drug that is effective without untoward toxicity. Phase III trials assess an optimal dose of the new drug (selected from Phase II results) in comparison to a placebo (“sugar pill”), or in comparison to best available standard treatment. Safety and efficacy are the hallmarks of Phase II/III trials, conducted in a highly structured environment where patients are closely scrutinized and observed by personnel (nurses and others) trained in the conduct of clinical trials.

It is unusual if more than a few thousand individuals are exposed during the 3 phases of drug development and, therefore, the toxicity of many drugs (e.g., Vioxx®) may not become obvious until they are marketed, when they are used by a much wider population. The exclusion from

Phases I-III studies of patients with diseases other than the one being studied, and those patients taking potentially interacting drugs further limits the likelihood that some drug toxicities will be uncovered. Indeed, until many more patients are exposed in “real world” situations, it is not possible to determine the true safety profile of a drug, device, or biologic agent.¹⁰ FDA is provided with “authority to monitor the progress of a post-marketing study commitment that an applicant has been required or has agreed to conduct by requiring the applicant to submit a report annually providing information on the status of the post-marketing study commitment.”¹¹ In September 2004, the FDA reported that over 800 post-marketing commitments were pending.¹¹ A focus of much of the concern articulated by the IOM is the absence of a commitment by all stake-holders to studying new drugs and devices over their entire “life-cycle”.¹ Congress has also expressed its interest in studies over the life-cycle of drugs (and biologics and devices), as described in newly passed legislation, the Food and Drug Administration Amendments Act of 2007 (FDAAA), which the President signed into law on September 27, 2007 (Public Law No. 110-85).¹²

There is widespread agreement that, if not “broken,” the current passive system is inadequate and requires at the very least a new emphasis on active surveillance and aggressive pursuit of Phase IV testing of drugs/biologics/devices. Noblis, a not-for-profit science and engineering company working in the public interest, believes that this new paradigm^{13,14} can succeed only if enhanced by an overall systems approach and technical innovations for managing the system. Therefore, Noblis committed resources to studying the problem and bringing together a group of experts to respond to the IOM report with the development of an action plan.

2.2.1 Patient/Volunteer Health Organizations (VHO) Response

Pharmacovigilance during the post-licensing phase of a product’s lifecycle is usually framed in terms of safety and efficacy. However, patients suffering from serious conditions more often focus on a risk/benefit calculation for a product. They are aware that there are risks associated with any medication, biological agent, or device, and rather than restricting or removing the product from the market, they would prefer full and detailed information about risks and benefits, and then privately, with their physician, make a decision about whether or not the

product is right for them. The National Health Council, an umbrella group representing VHO's, and the Arthritis Foundation, have responded by advocating for access to new treatments; full, unbiased public disclosure of the risks associated with products; and against regulatory or legal impediments that restrict patients and their physicians from weighing the risks and using products that are effective for them personally. Advocacy groups for patients with chronic conditions naturally push for more funding for research into cures, but it is clear that information about risk/benefit profiles of existing products derived from post-licensing research are of paramount interest to them.

2.2.2 United States Congressional Response

With the introduction of S.3807, the Senate version of the original legislation that resulted in Public Law No. 110-85, its sponsors, Senators Mike Enzi (R/Colorado) and Edward "Ted" Kennedy (D/MA), signaled their desire to deal preemptively with the recommendations of the IOM panel.¹⁵ Senator Kennedy said that "Like the Institute of Medicine report, our bill emphasizes the need for a 'life-cycle' approach to drug regulation, both before and after approval." The Reagan-Udall Institute for Applied Biomedical Research, recommended in Title II of the original legislation, is designed to stimulate innovative approaches by a public-private partnership to "advance the Critical Path Initiative" and improve the sciences of developing, manufacturing and evaluating the safety and effectiveness of drugs, devices, biologics and diagnostics." The Critical Path Initiative is FDA's effort to stimulate and facilitate a national effort to modernize the scientific process through which a potential human drug, biological product, or medical device is transformed from a discovery or "proof of concept" into a medical product. S.3807 also called for the creation of a structured framework for resolving post-licensing safety concerns (e.g., required registries, epidemiologic studies, clinical trials) and guidelines for management of conflict of interest and FDA Advisory Committees.

2.2.3 FDA Response

Prior to the release of the IOM report,¹ the FDA had developed several new initiatives that in many ways predicted the recommendations of the IOM panel. Among their recent efforts of relevance are the Critical Path Initiative begun in 2004, a collaboration with the Critical Path Institute (CPI),¹⁶ and a collaboration with the Massachusetts Institute of Technology (MIT).¹⁷

The FDA Critical Path Initiative is designed to translate basic research more rapidly into clinical benefits for patients with a list of Critical Path Opportunities in six key areas: (1) development of better evaluation tools (biomarkers and disease models); (2) streamlining clinical trials; (3) harnessing bioinformatics; (4) moving manufacturing into the 21st century; (5) development of products to address urgent public health needs; and, (6) development of products designed for at-risk populations.¹⁶ The Critical Path Initiative is now being extended to all FDA-regulated foods and animal products. The FDA is partnering with the CPI in Tucson, Arizona,¹⁶ the Center for Biomedical Innovation (CBI) at MIT,¹⁷ and Duke University to stimulate the development or adaptation of “proven biomarkers, innovative clinical trial designs, simulation models of physiology and disease processes, and manufacturing quality assessment methods - - capable of rapidly predicting the safety, effectiveness, and quality of new medical products.”¹⁶ The FDA has developed additional partnerships with the Department of Defense (DoD), the Department of Veterans Health Affairs (DVHA), the Agency for Health Research and Quality (AHRQ), the Centers for Disease Control and Prevention (CDC) and other government and non-governmental organizations (NGOs), for the purpose of enhanced surveillance of new drugs, devices, and biologics, and this kind of private-public cooperation will be greatly enhanced by the recently created Reagan-Udall Foundation.

2.2.4 Industry Response

The pharmaceutical industry shares the concerns of the IOM in regard to the need for a better system for monitoring the safety of approved drugs (and, by analogy, biologics and devices).⁸ The Pharmaceutical Research and Manufacturers of America (PhRMA), however, does not see the magnitude of the problem in the same light as the IOM, pointing to a similar total number of drug withdrawals in the recent past as compared with historical data. However, of greater concern to PhRMA is the other end of the process - the pipeline for new drugs, which appears to be failing.¹⁶

As noted by Horrobin, “Total worldwide new chemical entities launched each year have fallen from 80-100 per year in the 1960s, to 50-60 per year in the early 1980s, and 30-40 per year in the late 1990s.⁷ In 2004, the number dropped to a 20-year low in the U.S. of 22 new drugs. While these two problems (drug safety and new drug discovery) may not seem so clearly linked, they are very much part of the same problem. The pharmaceutical industry has become extremely risk-averse in the post-Vioxx era and continues to systematically turn away from investing heavily in testing drugs with novel mechanisms of action in favor of adding variations to well-tested classes of drugs (e.g., statins). It is very likely that a systems change that contributes to an improved ability to predict safety and efficacy will facilitate new drug development by enabling “tailored therapy for each patient.”¹⁶

In March, 2006, the FDA announced a collaborative project with five large pharmaceutical companies, and in August, 2006, a collaboration with the CBI consortium at MIT, which includes Altana Pharma, Astra-Zeneca, Brain Resource Company, Bayer AG, Eli Lilly, Gene Logic, Merck and Novartis, to develop new biomarkers and speed the process for earlier validation of therapeutic targets and methods for monitoring safety and efficacy. The industry clearly understands the need to link safety and discovery.

The speakers from industry at the Forum described wide-ranging programs to track the safety of their products throughout the entire product lifecycle. The numbers of employees involved in comprehensive safety programs within pharmaceutical companies is large. For example,

Dr. Mitchell Gandelman of Pfizer gave a figure of over 2,000 such individuals, and Dr. Amrit Ray's detailed description of how safety accountability is managed at Bristol-Myers Squibb demonstrated both the complexity of the systems needed to accomplish the task as well as the significant resources required. The speakers made it clear that patient safety, beginning with clinical trials and extending as long as the product is prescribed, is the focus of their extensive programs. Moreover they believe that the ability to predict drug safety, efficacy, and risk will also stimulate innovation and new drug development.

Companies' efforts to implement such programs focused on a number of facets, some of the most prominent being:

- Re-engineering of their internal adverse event reporting and processing
- Clear assignment of safety accountability for each product at each point of its lifecycle
- Science-based improvements in the analysis of adverse event data
- Educational resources for physicians and patients
- Improvements in the execution of post-approval studies

2.2.5 Investigator Response

The scientific requirements for implementing a coherent, effective, national (or international) pharmacovigilance program are varied. Dr. Richard Platt of Harvard University gave a high-level view of data warehousing to support a distributed research network, which highlighted both the distributed nature of the data set and the need to query it in a variety of ways depending on what is needed and how it will be used. Designing and implementing an information technology (IT) infrastructure to support active surveillance poses challenges that involve data management research and domain specific computational research such as processing of natural language texts. The design of the data resource and the mechanisms for granting access rights will be tightly interlinked with the need to develop research protocols and methods that effectively make use of the data being warehoused. Whereas the systems described for Pfizer and Bristol-Myers Squibb can be managed in a way that serves the specific needs of the companies, a multi-stakeholder, distributed data resource would be serving all the stakeholders in

ways that are meaningful to each. The success of the manufacturers in designing and implementing whole-life-cycle, corporate pharmacovigilance systems indicates that information technology is not an insurmountable bottleneck when designing and implementing a national or even global pharmacovigilance network.

Assuming a future state where impediments to information flow are removed, the next question researchers ask is, “how would these data be analyzed and utilized?”

Areas of focus mentioned by Dr. Platt are:

- Assessment of data quality
- Utilization studies
- Retrospective outcome studies
- Prospective surveillance of outcomes

As researchers move forward with the conviction that the problem of data access will be overcome, the questions shift to how we can best design and ramp up active surveillance programs while improving spontaneous surveillance so that the two become complementary facets of an integrated pharmacovigilance program.

2.2.6 Provider Response

The Veterans Healthcare Administration (VHA) electronic health record (EHR) system provides a clear demonstration of the technical feasibility of EHRs as well as the numerous benefits they provide. When trying to envision a future state of healthcare, one of the first things that most people include on their lists is an EHR. During the forum’s presentation by Fran Cunningham, Director, Center for Medication Safety, Veterans Health Affairs, she noted the VHA electronic health record as one of the key elements for the success of the VHA pharmacovigilance system. She noted other critical aspects that contribute to this success of their system, such as clinicians who are committed to the new system and enforcement. While the VHA is a closed provider system as compared to private sector provider systems, it was noted there are valuable lessons to be learned from the VHA experience. For example, if a patient has an adverse reaction to a

medication, this is recorded in the EHR and if at any time in the future, a doctor attempts to prescribe that medication, the system is able to generate a warning.

2.3 Future State

During the forum, various components of the future state were envisioned as potential solutions to the problems discussed. It is clear that all stakeholders have committed significant resources to solving facets of the problem that they find most urgent. But the challenges to building a well-functioning pharmacovigilance system are not just technical. For example, the successful IT efforts by the VHA and the pharmaceutical companies clearly demonstrate that IT is not an insurmountable barrier to a well-functioning pharmacovigilance infrastructure. The core barriers to a Patient-Focused system, articulated by the participants, are:

- Lack of access to information
 - E.g., What kinds of information should be available to patients and how will they get it?
 - If patients, either individually or through VHO's, are fully participating in the system, then how should the information they provide be captured and effectively used?
 - How can shared information be protected?
- Lack of clarity about funding or cost-sharing
 - E.g., Who should pay for post-licensing surveillance and research activities?
 - Who should pay to support an infrastructure that makes it possible for any qualified stakeholder to access information owned by other stakeholders?
 - How can owners/aggregators of information be compensated when they share it?
- The legal and regulatory environment has not been focused on Patient-Focused pharmacovigilance. Examples of questions that arise are:
 - Which patient focused concerns does the FDAAA address and which not?
 - What legislation is needed to provide a legal and regulatory environment that supports and protects the necessary information flows?

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- What is needed beyond the FDAAA to accelerate the patient focused reform of post-licensing research?
 - What can be done to address the patient's need for detailed, understandable information about risks and benefits of treatments
 - Required disclosure of data suggestive or an indication of safety issues.
 - Not all large scale serious side effects were unknown by the manufacturers. What is the appropriate deterrent for this type of behavior? How can the disclosure requirements be constructed to encourage and support early reporting of problems and conversely, apply punishment at the required level of severity to discourage/penalize manufacturers that intentionally minimize, hide or deny safety issues?

Some specific elements of a future state related to post-marketing surveillance addressed at the forum were:

- Public Education, as has been recently advocated regarding science in general by Dr. Alan Leshner, the Chief Executive Office of the American Association for the Advancement of Science (AAAS)¹⁸
- User Friendly Electronic Methods
- Acceleration of initiation and completion of Phase IV Post Licensure Surveillance Studies
- Opportunities for Transformation

2.3.1 A Public Education Program

A program to increase awareness of the drug/biologic/ device development process to seek active public participation in post-licensing surveillance (PLS) should be the cornerstone of new FDA programs for monitoring post-licensing safety and efficacy. In addition, scientific training programs in clinical and translational research at academic institutions and FDA should be fortified with the goal of developing methodologies that can improve the skills of the science establishment's ability to reach out to the public, as has been developed by the Aldo Leopold

Leadership Program and Research America's Paul G. Rogers Society for Global Health Research.¹⁸

The medical community also needs to be much better informed about the existence and purpose of the pharmacovigilance system and the value of spontaneous reporting. Health care professionals' education about pharmacovigilance should begin in medical school and continue for their entire career.

2.3.2 User-Friendly Electronic Methods

User friendly electronic methods for tracking product risk, efficacy, and safety should be developed and implemented so that patients and their physicians can remain informed as to the progress of post-licensing studies and participate to the fullest extent possible – without sacrificing efficient medical practice.

2.3.3 Phase IV, Post-Licensing Surveillance (PLS) Studies

The PLS studies should be designed as appropriate extensions of Phase III studies and be required for all new drugs, biologics, and devices. Initially, it may be possible to only apply this approach only to drugs, biologics, and devices with unique mechanisms of action. However, ultimately it would be ideal to require such trials for all new drugs. New paradigms for collecting and analyzing data from Phase IV trials may be necessary to account for low “signal to noise ratios” likely to be generated in the presence of complex variables, usually eliminated by exclusion criteria in Phase III studies. Finally, such studies should remain within the jurisdiction of independent research scientists and biostatisticians and funded by the research arm of the pharmaceutical industry and not as an extension of marketing efforts. The current efforts of the FDA to bring science back to PLS is to be applauded and supported. The call for reform of the process for PLS of new drugs, biologics and devices was borne out of critical review of existing surveillance systems, and therefore carries with it some negative connotations. Viewed another way, efforts to reform PLS will prove to be an extremely powerful catalyst for the changes and improvements being called for in other dimensions of healthcare. Thus, when evaluating the benefits and risks associated with the development of a robust PLS process for drugs and

devices, it is essential to consider the full range of benefits – which are opportunities – especially in the context of how they contribute to healthcare improvement efforts going on elsewhere.

Phase IV trials represent only the most obvious point of contact between the world of pharmacovigilance and the world of Evidence-based Medicine (EBM), due to the fact that both are focused on the science of medicine. But there are other aspects of these two pursuits that suggest even greater synergy. For example, a central focus of EBM is to provide scientifically informed, Patient-Focused care, so one way that pharmacovigilance can contribute to this is by providing detailed risk information that makes it possible for providers to discuss alternative treatments to patients with serious conditions, who may be willing to take risks for specific benefits.

2.3.4 Opportunities for Transformation

There are at least five areas of benefit and opportunity, in which a robust post-licensing research and surveillance program would fuel faster and deeper changes in healthcare, in general.

2.3.4.1 Confidence

There is need to improve public confidence in the current mandate for PLS because the studies are not always performed and, when they are performed, are often carried out by the marketing departments of drug, biologic, and device companies. If PLS research were conducted with the same academic and scientific rigor as Phase I, II, and III trials, a great deal of confidence could be restored to the drug, biologic, and device industry.

2.3.4.2 Safety/Risk/Benefit

Post-licensing surveillance is mainly concerned with safety. However, as the art and science of patient safety are maturing, mechanisms for improvement in safety and for support of informed patient choice regarding risk would be greatly served by a mature pharmacovigilance system.

2.3.4.3 Economy

It is difficult to know how much money is wasted each year treating patients with FDA.- approved drugs or devices that either do not work as effectively as they should or perhaps even harm some patients. Knowledge acquired via pharmacovigilance would provide opportunities to leverage the dollars spent as effectively as possible to improve patient care and reduce waste.

2.3.4.4 Transparency

As healthcare becomes more consumer-driven, efforts are underway to simplify publicly available information so that consumers can make easy and confident healthcare decisions (e.g., right or wrong, good or bad). This call for greater transparency and clarity of information that was historically concealed and complex is affecting all involved in healthcare. 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

2.3.4.5 Satisfaction

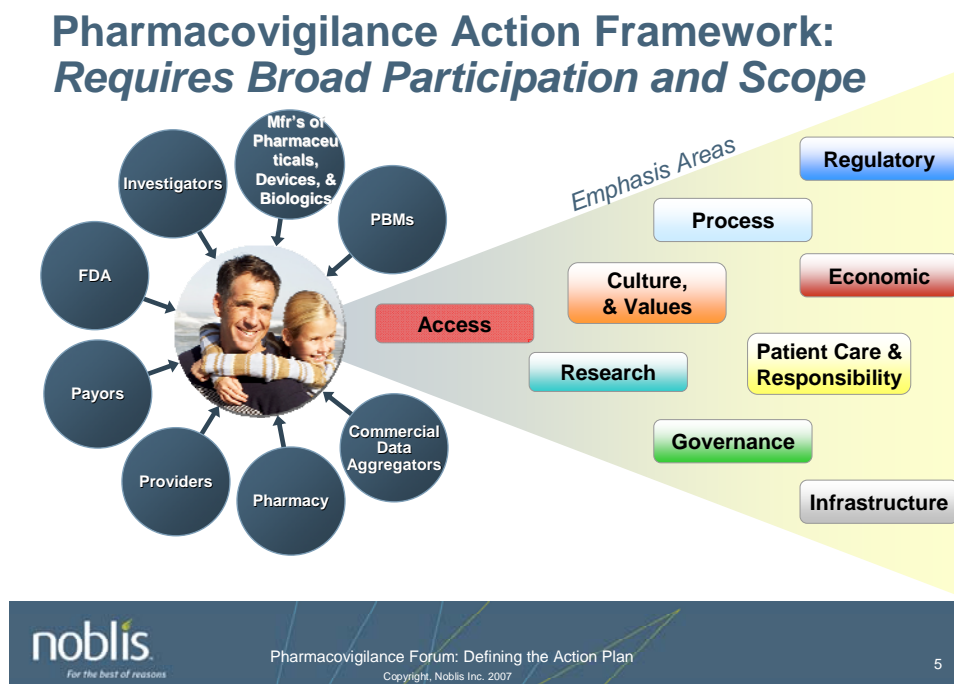
After all is said and done, in the pursuit of measuring healthcare performance, quality may be in the eye of the beholder. And, as is being learned in quality circles, the best definition of quality may be the level of consumer satisfaction. But because most consumers are still “lay people” and are not equipped to perform drug evaluation, other than providing data as appropriate (efficacy, ADE, or side effects) to their prescribing provider, accountability for the evaluation of safety and efficacy must first reside with the manufacturer, and subsequently, by the prescribing provider.

3. NOBLIS RECOMMENDED ACTION PLAN FOR NEXT STEPS

Introduction

As summarized above, there are tremendous opportunities and challenges to address the healthcare system domain of pharmacovigilance. The opportunity is to address both today's issues and work toward a desired future state that needs to continuously and intentionally evolve. We believe that the only stable future state, and indeed the only acceptable future state, will be attained by following the guiding principle of embracing a patient/person focused view.

The following figure illustrates the conceptual model discussed at the Forum, including the primary stakeholders and areas of emphasis. This conceptual model was confirmed by the attendees of the Forum with the addition of access to new therapeutic agents as an important area of emphasis.



3.1 Patient-Focused Pharmacovigilance Working Group Vision

During the forum, speakers and participants confirmed the value of conceptualizing the approach to address the problem by recognizing the different perspectives of the various stakeholder groups, identifying the areas requiring special emphasis, and the criticality of maintaining the vision of the healthy patient as the key goal of all endeavors. Furthermore, there appeared to be an appreciation that the only way to make progress in pharmacovigilance is by collaboration and sharing of responsibilities amongst the stakeholders. The need for, and value of, a Patient-Focused Pharmacovigilance Working Group (PFPWG) is clear as a result of discussions at the Forum. This has been reinforced in discussions since the Forum and these discussions have brought about greater clarity as to the scale and scope of the issues the PFPWG should tackle. As participants shared their knowledge, a number of other initiatives were discussed, but the consensus was that a group representing the patient point of view would complement and help integrate other efforts around the organizing principle of putting patients' needs and concerns first. Examples of other initiatives and entities addressing different aspects of the pharmacovigilance problem identified during the forum were:

- Integrated VA DB - 2002-03
- Center for Medication Safety 2004-06 Risk Reduction Program
- Adverse Drug Event DB (VA ADERS)
- Adverse Reaction Tracking Package (ART Package)
- Vaccine safety data link w/ CDCMedSun: 350 Healthcare Facilities (voluntary reporting of adverse reactions)
- NEISS: ER data surveillance (w/ CDC, CPSC)
- FDA MOU's with DOD and VHA
- Multiple partnerships with groups having access to eHRs
- PhRMA Observational Medical Outcomes Pilot
- Predictive Safety Testing Consortium (PSTC)

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- Variety of Public-private Consortia and International efforts

The PFPWG will collaborate with other pharmacovigilance entities and initiatives worldwide to leverage the work of others, minimize redundancy of effort, and yield more timely benefits.

3.2 Approach and Organization Moving Forward

The goal of the proposed Patient-Focused Pharmacovigilance Working Group is to address the complex problems discussed at the Noblis Forum for Pharmacovigilance with a patient focused view that also complements and collaborates with the efforts of other groups internationally. Representation of all stakeholders in the PFPWG is critical, including public and private, government and non-government, academic, patient advocacy, and industry sectors. Research and political awareness will be integral to the PFPWG, with further development of this concept required. Additional stakeholders may be identified, e.g. the Centers for Disease Control. To date, additional stakeholders representing public health and pharmacovigilance economics have been identified and will be included in future efforts. It is critical that the key stakeholder groups and sectors noted above are each represented in working teams created to focus on specific issues.

The proposed organization of the Patient-Focused Pharmacovigilance Working Group (PFPWG) moving forward is:

- an Advisory Board
- a core Integration Team, and
- Focus Teams that formed as needed to address specific issues.

Based on the Pharmacovigilance Action Framework, the following aspects of the entire system that will need to be considered by a Focus Team when tackling any specific issue:

- Regulatory/Economic/Governance
- Research
- Process/Infrastructure

-
- Access/Risk/Culture/Values/Patient Care/Responsibility

3.2.1 Advisory Board Role

The Advisory Board will be comprised of executive leaders from both public and private organizations who will serve in providing objective review and comment on the work of the Integration Team and the issue-specific Focus Teams. The Board will convene semi-annually, and it is envisioned they will be available for ad hoc requests by the Focus Teams in specific areas where their insights would be needed.

3.2.2 Integration Team Role

The Integration Team will provide leadership for the PFPWG and ensure frequent communication internally, externally and with all stakeholders as appropriate by addressing:

- Governance, infrastructure, and administrative needs
- Coordination with the PFPWG Advisory Board
- Collaboration with other Pharmacovigilance entities and activities
- Education and issue resolution
- Fundraising to support the PFPWG activities, and most importantly....
- Creation of current, transitional, and future state Patient-Focused Pharmacovigilance System Models that integrates the work of the Focus Teams

Noblis is committed to taking the lead with the core Integration Team. The commitment of time, talent, and/or funding from *all* stakeholders is needed to accomplish the objectives of the PFPWG. Proposed sub-teams of the PFPWG Integration Team and their responsibilities are as follows:

3.2.2.1 Administration

- Raise funds to support and create necessary infrastructure, research, education, and communications among stakeholders

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- Set up regular communications plan and schedule for PFPWG
 - Develop strategic plan for the PFPWG
 - Create and monitor master plan and issues list
 - Plan and maintain 15 month revolving schedule
 - Develop and maintain Advisory Board
 - Work with Focus Teams to establish standard tools, processes, and communication to ensure effective and timely communication

3.2.2.2 Outreach

- Support collaborations of stakeholders where immediate benefits can be gained such as with DoD, AHRQ, NIH, FDA, VHA, CMS, and CDC
- Collaborate with Voluntary Health Organizations (VHOs) to enlist their involvement and support in ensuring all aspects of a patient-focused view are addressed.
- Leverage lessons learned from expansion and integration of Department of Defense Military Health System and Veterans Affairs Pharmacovigilance program(s) and with other agencies; and
- Develop and implement Congressional liaison plan.

3.2.2.3 Systems Modeling

As Focus Teams work through specific issues, a key aspect of their results will be a contribution to the development of systems dynamics models that help clarify connections between elements of the system as well as how changes to one part of the system affects the other parts. The Integration Team would support the merging of individual parts into a “system of systems” model. Well-established techniques and tools are available that make it possible to model very complex systems, with the goal of understanding their dynamics. Modeling both the current state as well as a potential future state will support the PFPWG

in thinking about how to transition from the former to the latter and possibly provide insights into how to achieve near term benefits for patients. Such models would include:

- Patient-Focused pharmacovigilance infrastructure that includes interactions between stakeholders
- The information needed to support a well-functioning system, including types of information; how it needs to be used; who the authors, owners, and users of the information are; and how it relates to other information
- Economic impact (cost/benefit) for current and future states
- The legal and financial influences on the system, with emphasis on identifying barriers to development of an effective, Patient-Focused national pharmacovigilance system, e.g., patent issues, incentives for early reporting of safety signals
- Aspects of communication of key risk/safety/efficacy information to patients and other healthcare delivery professionals, Payors, Pharmaceutical Benefits Management (PBM) plans, etc.

3.2.3 Focus Teams

At this early stage in the development of the PFPWG, there are a seemingly overwhelming number of issues and recommendations identified, but inherent and central to any Patient-Focused view of pharmacovigilance is the access for patients. “Access” means, for example, more comprehensive access to drugs (at various stages of testing), access to information pertinent to risk vs. benefit decisions at different stages of testing and/or disease, transparency and opportunity to provide input to decision-making by government regulators affecting drug availability, etc. In its broadest sense, “patient access” is a cornerstone of a Patient-Focused system. Assuming the first Focus Team of the PFPWG tackles the topic of patient access, potential questions/issues to be addressed are:

3.2.3.1 Regulatory/Economic/Governance

- Analyze and recommend how manufacturers of therapeutic agents might be required to communicate risk/benefit information to patients.
- What controls are needed to provide patient access and still protect patient privacy rights?
- Analyze how early access to new drugs would impact product liability and determine how that will impact manufacturers, payors, PBMs, pharmacies, physicians, and patients.
- For any proposal that increases patient access, analyze and recommend who should bear the cost that falls on the pharmacovigilance network.
- Analyze and recommend how data property rights should be honored (e.g., payors, pharmacies, PBMs, data aggregators, etc.) without impeding the flow of crucial information.
- Quantify the increased costs of any proposed change to the Pharmacovigilance Network to stakeholders.
- Analyze and recommend methods for financing a larger number of Phase IV trials, or a system of expanding trials that provide drug and/or information access to an expanding group of patients.
- Analyze and recommend how patients/patient advocacy groups should be integrated into Pharmacovigilance governance process.
- Analyze how patient advocacy groups might help prioritize the Phase IV studies that need to be done.
- Explore policy and regulatory frameworks that could drive the Evidence Based Medicine community, the pharmacovigilance community, and the community of researchers carrying out clinical trials towards the single goal of science-based, Patient-Focused medicine, with information about all phases of a drug's lifecycle available to patients

3.2.3.2 Research

- Develop a mechanism for involvement of voluntary health organizations (VHOs) in design, implementation, analysis, and communication of results of Phase IV safety and efficacy trials – work thru NHC/FDA/Industry consortium.
- Analyze the technical issues regarding use of longitudinal EMRs (e.g., VA, DoD) to build models of health history that can be used to help weight signal strength.
- Determine how research information throughout the drug lifecycle could be effectively communicated to providers and patients.
- Analyze the issues of using large sets of EMRs to refine risk/benefit assessments for use in decision making by patients.

3.2.3.3 Process/Infrastructure

- Analyze and recommend how signals should be resolved, and how information about them should be passed back to providers and patients (especially to those who are reporting the event)
- If a patients want to directly report adverse events to CDER, should they be able to request that CDER gain access to their EMR?
- Analyze and recommend under what conditions access should be granted to the data
- Review VHA's protocol related to limiting drugs that have shown some issues, while allowing others to continue use, for wider application across the Pharmacovigilance arena.
- Define the optimal information to be presented to physicians (and how to present it) from a credible, trustworthy source at the point of prescribing a new therapeutic agent (drug, biologic or device).

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- Analyze and recommend how the infrastructure should facilitate patient access to risk information.
 - Analyze and recommend how the infrastructure should facilitate patient access to Phase IV trial information.
 - Identify infrastructure/systems available within VHA and DoD that could be useful externally to support patient and provider participation
 - Evaluate how Semantic Web technology can contribute to making data available to the various stakeholders who should have access to it
 - Evaluate what, if any, infrastructure might be helpful in fostering the interaction of the Evidence-based medicine community with the pharmacovigilance community

3.2.3.4 Culture/Values/Responsibilities

- Understanding the optimal level/amount/form of risk information, from a sociological viewpoint, needed by patients regarding therapeutics or devices.
- Examine how patients use existing resources to guide their own healthcare and seek to understand which resources serve which population subgroups best
- Understand the optimal communication mechanisms and access for conveying adverse drug events (ADE) and risk to patients

We propose that Pharmacovigilance Working Group sessions meet quarterly, with all members of each team dedicating an entire day.

3.2.4 Closing Statement

The Patient-Focused Pharmacovigilance Working Group has the potential to play a significant role in the transformation of the entire pharmacovigilance system. By focusing on the patient's view of healthcare and closely collaborating with other Pharmacovigilance initiatives, the

PFPWG will be able to help all stakeholders understand how to accommodate the needs of patients as they work together to develop a well-functioning system. Nothing short of a Patient-Focused approach will be needed to restore the public confidence, to improve access, to educate and inform, to ensure transparency of the system, and to support the FDA and other supporting organizations in providing the public with the highest level of service.

Given the support expressed by participants in the Forum on Pharmacovigilance, the call to action is clear. The immediate next step is a response to this white paper and implementation of the 2008 plan consisting of four PFPWG meetings, the next to be held in April 2008, and formation and work of the Advisory Board, Integration and Focus Teams initiated; development and implementation of a master plan and fundraising to support these efforts. The need for addressing the Pharmacovigilance problem is clear. The call to action is now!

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APPENDIX A : PARTICIPANTS

SPEAKERS/TOPICS:

Amr ElSawy, Executive Vice President, Noblis – “Patient-Focused Pharmacovigilance. A Roadmap Forward”

Ed Wyatt, EWyatt Consulting – “Patient-Focused Pharmacovigilance – Today’s Plan of Action”

Frederick R. Rickles, Fellow, Center for Science and Technology, Noblis – “Pharmacovigilance Conceptual Framework: Defining the Goal”

David Korn, Executive Vice President, American Association of Medical Colleges – “The Future of Drug Safety”

S. Ward Casscells, Assistant Secretary of Defense/Health Affairs – “DOD Pharmacovigilance Program: An Integrative Approach”

Fran Cunningham, Director, Center for Medication Safety, Veterans Health Affairs – “Drug Safety and Pharmacovigilance in the Department of Veterans Affairs: National Overview”

Marc Boutin, Executive Vice President, National Health Council – Pharmacovigilance and the Patient-Point-of-View”

Janet Woodcock, Deputy Commissioner and Chief Medical Officer, Food and Drug Administration – “Emerging Surveillance Mechanisms: View from the FDA”

David Bowen, Chief of Staff, Committee on Health, Education, Labor and Pensions (HELP), US Senate – “Current Status of Legislation on Drug Safety and Efficacy”

Amrit Ray, Vice President, Global Pharmacovigilance and Epidemiology – Medical Safety Assessment, Bristol-Meyers Squibb Company – “Developing Mechanisms for Pharmacovigilance – An Industry Perspective”

Patience White, Chief Public Health Officer, Arthritis Foundation – “Developing Mechanisms for Pharmacovigilance”

Curt D. Furberg, Professor, Division of Public Health Sciences, Wake Forest University School of Medicine – “Scope of the Problem and What Should Phase IV Studies Look Like in the Future?”

William B Mattes, Critical Path Institute – “Biomarkers, Pharmacovigilance, and C-Path’s Predictive Safety Testing Consortium”

Mitchell Gandelman, Vice President, Global Risk Management, Pfizer, Inc. – “Putting the System Together – A Public/Private Partnership”

Richard Platt, Professor and Chair, Department of Ambulatory Care and Prevention, Harvard Medical School – “The Way Forward in the Absence of Uniform Electronic Medical Record”

John Grabenstein, Senior Director, Merck Vaccine Division – “Active Community-Based Surveillance After Smallpox Vaccination via Telephone/Internet Diary, U.S. Department of Defense, Feb-Aug 03”

DISCUSSANTS:

Jeff Allen, Director of Science Policy, Friends of Cancer Research

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