

Institute for Alternative Futures

Optimal Futures for Risk Evaluation and Mitigation Strategies (REMS)

Workshop Report

March 4, 2010



Explore. Aspire. Create. Evolve.

The Institute for Alternative Futures (IAF) is a nonprofit research and educational organization founded in 1977 by Clement Bezold, Alvin Toffler and James Dator. IAF helps organizations monitor trends, explore future possibilities, and create the futures they prefer. IAF draws on a robust selection of futures methodologies, such as environmental scans, forecasts, scenarios, visioning and its own "aspirational futures" technique. Past clients include the World Health Organization, the Department of Health and Human Services, the Environmental Protection Agency, as well as a wide range of corporate clients through its for-profit subsidiary, Alternative Futures Associates (AFA). For more information, write to futurist@altfutures.com, visit www.altfutures.com, or call us at (703) 684-5880.

The Society for Women's Health Research is a national non-profit organization whose mission is to improve the health of all women through advocacy, education and research. Founded in 1990, SWHR brought to national attention the need for the appropriate inclusion of women in major medical research studies and the need for more information about conditions affecting women exclusively, predominately, or differently than men. SWHR advocates for increased funding for research on women's health; encourages the study of sex differences that may affect the prevention, diagnosis and treatment of disease; promotes the inclusion of women in medical research studies; and informs women, providers, policy makers and media about contemporary women's health issues. Visit SWHR's Web site at www.womenshealthresearch.org for more information.

Disclaimer: The views expressed in this report are those of the Institute for Alternative Futures and/or the Society for Women's Health Research and not necessarily those of workshop participants or their respective organizations.



Table of Contents

Introduction.....	1
REMS Past & Present	2
Appreciative Inquiry	4
1. <i>Post-Approval Studies and Special Labeling Communications.....</i>	<i>4</i>
2. <i>Restricted Distribution Programs.....</i>	<i>6</i>
3. <i>Monitoring, Testing and Special Populations</i>	<i>9</i>
4. <i>Product Quality Safety Studies</i>	<i>11</i>
The Optimal Future for REMS: An Agenda for Action	13
Appendix A: Workshop Participants.....	17
Appendix B: Background Information for REMS Groups	19

Introduction

The creation of Risk Evaluation and Mitigation Strategies (REMS) as part of the Food and Drug Administration Amendments Act of 2007 (FDAAA) marked a significant moment in the regulation of drugs and biological products. FDAAA gives the FDA broad powers to control drug marketing and labeling, to require post-approval studies, to establish active surveillance systems, and to make clinical trial operations and results more visible to the public.

While REMS are limited to risk communication plans and other specific elements to assure safe use of medicines that may pose safety risks, they combine with other elements of FDAAA, such as post-approval studies and labeling requirements, to create a new regulatory and safety environment. The significance of these measures expands further still when one takes a systems perspective that includes other trends in health care, such as legislative proposals to reform the healthcare system, meaningful use of electronic medical records (EMRs), integration of medical data, globalization of drug development and manufacturing, and changes in disease paradigms and care modalities. The difference between an optimal future for REMS and a more challenging future may depend on our ability to approach REMS from this systems perspective.

This report seeks to provide all stakeholders with the knowledge of what REMS are, but also of what REMS means as part of FDAAA and as part of the larger evolution of the healthcare system. Taking a systems perspective implies that all stakeholders have some responsibility for the outcome. Understanding the possibilities that REMS represents will enable stakeholders to work together to chart a pathway to an optimal future for REMS.

This report is based on a September 22, 2009 workshop sponsored by the Society for Women's Health Research and facilitated by the Institute for Alternative Futures. Participants represented four stakeholder groups: industry, regulators, academia, and consumer advocates. (A list of participants is provided in Appendix A.)

Participants were divided into four groups, each tasked with considering the optimal future of REMS in a different area. The first three groups addressed: post-approval studies and special label communications¹; restricted distribution; and monitoring, testing, or special populations. As a means to consider how REMS concepts may one day be applied beyond the limits of FDAAA, the fourth group was asked to consider how REMS might address product quality safety studies. (Background information given to each group is provided in Appendix B.) While some of the concepts discussed in this report extend beyond what is currently included in the REMS statute or even in the entirety of FDAAA, envisioning the optimal future requires consideration of the evolution of the healthcare system as a whole.

Each of these groups used the “appreciative inquiry” method to consider how REMS concepts and measures could be optimally applied in the future in their area. This method starts with a successful example from the past, then asks what elements of that example could also be applied

¹ The reader should note that post-approval studies and labeling are not explicit components of REMS, but are covered by separate FDAAA provisions; they are combined here in order to assess their cumulative effect.



in the future. This process resulted in a list of recommendations for stakeholders to address in order to create an optimal future for REMS.

REMS Past & Present

After the highly publicized Vioxx withdrawal in 2004 led to calls for fundamental changes in the nation's drug safety system, Congress passed the Food and Drug Administration Amendments Act of 2007 (FDAAA). Taking effect on March 25, 2008, FDAAA gives FDA broad powers to control drug marketing and labeling, to require post-approval studies, to establish active surveillance systems, and to make clinical trial operations and results more visible to the public.

One notable component of FDAAA is the FDA's new ability to require Risk Evaluation and Mitigation Strategies (REMS). Defined by FDA as a "strategy to manage a known or potential serious risk associated with a drug or biological product," a REMS may be required as part of a new drug application (NDA), abbreviated new drug application (ANDA), or biologics license application (BLA) where the agency deems it necessary to take additional steps to ensure that the product's benefits outweigh its risks. FDA can also require holders of approved applications to submit proposed REMS based on new safety information, such as a previously unrecognized or unlabeled risk or new findings concerning a known serious adverse drug reaction.

According to the statute, requiring REMS as a condition of approval allows the agency to mitigate risk based on assessments of such factors as: the size of the patient population; the seriousness of the disease or condition treated by the drug; the expected benefit; the duration of treatment; the seriousness of any known or potential adverse events that may be related to the drug; and whether the drug is a new molecular entity.

Under FDAAA, FDA has discretion to determine when REMS are necessary and what components of the REMS program to require. All REMS must include a timetable for assessments. If FDA makes the required finding, it can also require a Medication Guide or patient package inserts (PPI), a communications plan, or specific "elements to assure safe use." Such elements to assure safe use may entail: a training and certification program for prescribers and pharmacies; limiting dispensing to certain healthcare settings; only dispensing to patients with evidence of safe-use conditions; requiring patients and prescribers to enroll in a registry; and specific monitoring and testing of patients.

REMS provide an avenue for FDA to approve drugs and biologics that may otherwise have been held up indefinitely due to potential safety concerns that a REMS program can address. At the same time, REMS are now enforceable, meaning that FDA can declare a drug misbranded and impose civil monetary penalties if the manufacturer fails to comply with a requirement of the REMS program.

Since FDAAA went into effect in March 2008, FDA has required an increasing number of REMS, approving 32 in 2009 compared to just 24 approvals from April through December of 2008. While REMS approved in 2008 and in the early part of 2009 often have included only a Medication Guide, the FDA is increasingly requiring that REMS include a communication plan, elements to assure safe use, or an implementation system in addition to the Medication Guide.

It is important to note that FDA policy on REMS thus far has been developed on a case-by-case basis between the agency and the sponsor. However, FDA has taken steps to engage various stakeholder groups, such as holding a meeting on May 4-5, 2009, with healthcare providers and representatives of the pharmacy and patient communities to gather input on how REMS should be developed for specific opioids. FDA also held a public meeting on May 27-28, 2009 where more than 100 people provided suggestions on REMS for specific types of opioids. Furthermore, on September 30, 2009, the agency released draft guidance on REMS and for the first time provided the agency's current thinking on three important issues: the content of a proposed REMS submission; the conduct of REMS assessments and modifications of proposed REMS; and communications with FDA about REMS.

The evolution of REMS thus far raises questions of how broadly FDA intends to require REMS and what these plans will need to include, particularly in light of the agency's announcement of a planned class-wide REMS for opioid products and de facto class-wide REMS for tumor necrosis factor alpha (TNF- α) blockers and botulinum toxin. There are also questions about how REMS apply to generics, especially in cases where companies are required to develop, implement, and manage restricted distribution programs that are costly and require a substantial infrastructure to assure drug safety. Because REMS will evolve as healthcare systems are changing, all stakeholders in the safety of medicines will be affected.

A Systems Perspective

Because no stakeholder can see all of the impacts that a growing number of REMS may have, all stakeholders are called to be responsible for and responsive to a successful implementation of REMS policies. Each stakeholder group has different information, perspectives, and insights that together can be leveraged to develop and implement more effective REMS. The systems perspective requires that each stakeholder take responsibilities and play roles as follows:

- Patient/Consumer Advocates represent the needs of people who will ultimately receive the benefits from innovation or pay the price for unknown hazards. They are responsible for providing feedback to all other stakeholders about how well the system is serving patients and consumers.
- Regulators have the great responsibility to ensure public safety. The significant challenge for regulators is to ensure that the benefits of innovation are maximally available while the hazards are minimized.
- Sponsors have the responsibility to convert science into products that are appropriately valued in the marketplace. But value depends on the control of potential risks. Sponsors bear the primary responsibility for implementation and management of REMS programs, and this management entails commitment and direct control.
- Academics have the responsibility to bring unbiased knowledge about risk evaluation, mitigation, and communication to all other stakeholders, and to support continuous improvement and development.



- Prescribers have the responsibility to guide consumers and patients in making informed decisions about risks and to provide feedback when the risk mitigation system has become overly cumbersome.
- Pharmacists have a major responsibility to ensure that the consumer understands the risks and proper use of prescription drugs.
- Payers have a responsibility to ensure that benefit-risk decisions fit with the economic criteria that they set for value.
- Policy-makers have a responsibility to improve public health and to ensure that the intended effects of policy are realized and unintended consequences are addressed.

A systems perspective invites all stakeholders to see REMS not as simply another regulatory device but as one element of a larger evolution of the healthcare system. This perspective ensures that the optimal interests of all stakeholders are brought into the design of policies and procedures. A system perspective uses feedback from all parts of the system to ensure that the intent of improving public health is served by REMS as it affects the different stakeholders. As systems change – whether through healthcare reform, the adoption of new technologies, policies, procedures, or simply changes in the marketplace – the effects on REMS implementation will need to be understood.

Appreciative Inquiry

To stimulate thinking about the optimal future of REMS from this systems perspective, this workshop divided participants into four groups. The first three groups addressed post-approval studies and special label communications; restricted distribution; and monitoring, testing, or special populations. The fourth group addressed product quality safety studies; while this area is not currently under the purview of REMS, its inclusion provides a test case for how the thinking behind REMS could be further applied in the future.

Each group was asked to conduct an “appreciative inquiry,” starting with an example of a successful approach taken in the past, then identifying how the successful aspects of that approach could be applied in the future. This technique highlighted specific steps that, if taken, have the potential to lead us toward an optimal future for REMS.

1. Post-Approval Studies and Special Labeling Communications

One group addressed the implications of FDA’s new authority to require risk mitigation throughout the product cycle for any drug or biologic. This may include requiring post-market studies and new communications to alert patients and clinicians when studies reveal new risks. These post-market studies and labeling requirements are not included within REMS, but are covered by other statutes within FDAAA.

Before requiring a post-market study, FDA must determine that adverse event reporting and post-market risk identification systems are insufficient to evaluate whether the drug can be distributed and taken safely. When these situations apply, FDA requires sponsors to submit a timetable for conducting the study, providing periodic reports on the status of the study, including the number of participants enrolled and the expected completion date. FDAAA gives FDA the discretion to require the sponsor to make any changes to the label the agency “deems appropriate to address the new safety information.” Moreover, FDAAA confers authority to FDA to level civil monetary penalties if these post-approval studies are not conducted to the agency’s satisfaction or are delayed.

Recognizing the link between risk mitigation and REMS, this group began its “appreciative inquiry” with the example of FDA ordering studies to assess the incidence of blood clots and stroke in women taking a widely prescribed oral contraceptive containing drospirenone, which is known to increase potassium levels in the blood. Because higher blood potassium levels may increase the risk for cardiovascular events, FDA required a post-marketing study to determine the conditions under which this drug can be taken safely and what specific labeling and communications are required to mitigate the risks.

In designing the study, researchers enrolled a large patient population and engaged multiple stakeholder groups – the manufacturer, FDA, researchers, prescribers, and patients – in order to assess the effectiveness of different risk mitigation measures. The study found that almost 20% of women taking an oral contraceptive containing drospirenone were prescribed other medications that may increase blood potassium levels. As a result, FDA required new language in the labeling of birth control pills containing drospirenone to warn prescribers and patients of the dangers of combining these drugs. FDA also mapped out a risk management strategy including regular monitoring of the blood potassium levels of patients taking these contraceptives, patient information identifying drugs that are contraindicated, and physician-patient communications regarding the risks.

The group learned from this example that a systems approach to the design of post-approval studies and risk communications can significantly improve subsequent learning. Engaging multiple stakeholders at the beginning allowed this study to recognize factors that might otherwise have been missed influencing how and by whom risk information is communicated to different subpopulations.

To apply this learning for the future, FDA could set new guidance for the design of post-marketing studies to include assessing differences between subpopulations – e.g., sex, education, and health literacy – when determining strategies to mitigate risk. Particularly in light of developments in personalized medicine, a one-size-fits-all approach to study design may leave vulnerable patient populations underrepresented and conceal opportunities to mitigate risk. Accounting for biological differences between men and women and the special needs of patients with rare disorders where treatment options are limited is critical to research and the development of treatment options. This approach avoids increased costs and the need for additional resources to conduct populations-relevant post-marketing studies.

2. Restricted Distribution Programs

Certain drugs and biological products offer life-saving benefits but come with very high risks. They can be dangerous if not prescribed, administered, dispensed and taken appropriately. FDAAA provides statutory authority for FDA to require restricted distribution programs to ensure that the drug is only used by patients in whom a known serious or fatal risk can be avoided by proper use. Elements of a restricted distribution program may include physician qualification and registration, patient informed consent, and pharmacist distribution limitations, controls to ensure the safe return and disposal of unused medications, and warnings or precautions relative to a specific subpopulation or post-approval studies in such a population.

Because risk distribution programs must control the use of a drug or biologic from beginning to end, they are costly to develop, implement, and manage the infrastructure to assure safe prescribing, dispensing, and use of the drug. Patients must be monitored for early signs of safety issues and prescribers and pharmacists must be certified in order to dispense the medications and counsel patients. At the same time, these programs require coordination with the states, many of which have instituted donation and drug repository programs that allow medications to be re-dispensed to needy patients, potentially outside the restricted distribution program. Restricted distributions must address all these issues, while balancing patient access and patient safety and assuring that restrictions protect patient privacy and are not overly burdensome on prescribers and pharmacists.

With these issues in mind, this group began its “appreciative inquiry” by reviewing the development and implementation of the System for Thalidomide Education and Prescribing Safety (“S.T.E.P.S.®”), often considered the gold standard among restricted distribution systems. Developed by the Celgene Corporation and the FDA, S.T.E.P.S. strictly regulates the distribution of thalidomide. This drug modulates the production of an important cytokine (tumor necrosis factor alpha, or TNF- α) and is now approved in the U.S. to treat multiple myeloma and erythema nodosum leprosum (ENL), a painful complication of leprosy.

Previously, the drug was marketed in 46 countries outside the U.S. to treat anxiety, insomnia, and morning sickness. From 1956 to 1962, as many as 10,000 thalidomide babies were born with major birth defects, including a condition called phocomelia involving the severe shortening of the arms or legs with flipper-like hands or feet. Thalidomide also caused malformations of the eyes, ears, heart, genitals, kidneys, and digestive tract. Because of the potential for birth defects, thalidomide was not prescribed or sold until important therapeutic benefits were shown for patients with ENL, cancer and several other life-threatening diseases. For some time government agencies made thalidomide available to ENL patients through an Investigational New Drug (IND) application and the FDA agreed to establish “single patient” and “open protocol” IND’s so that physicians could use thalidomide to treat patients with serious illnesses. FDA began working with Celgene to develop S.T.E.P.S., a program of strict controls to regulate the distribution of thalidomide from beginning to end. Once S.T.E.P.S. was in place, the FDA approved Celgene’s thalidomide product, Thalomid®, for the treatment of ENL in 1996 and then



for multiple myeloma in 2006.

For Celgene to bring Thalomid to the U.S. market, the FDA required a restricted distribution system that would prevent fetal exposure to thalidomide. Thus, S.T.E.P.S was designed as a closed-loop performance-linked access system comprised of a complex network of database, fax, image storage, telecommunications and Interactive Voice Response servers where every aspect of thalidomide's distribution would be tracked, from the manufacturer to the patient.

Specifically, S.T.E.P.S. comprises:

- Mandatory pregnancy testing,
- Mandatory birth control,
- Physician and patient education using videotapes, brochures and other materials,
- Mandatory prescriber, pharmacist and patient registration,
- Mandatory patient informed consent and related certifications, and
- Controlled distribution.

Under S.T.E.P.S., no prescription is dispensed until all prerequisites have been completed and prescription authorization numbers have been issued. For women of childbearing potential, pregnancy tests must be performed within 24 hours of beginning therapy and then every week for the first four weeks of treatment followed by every two or four weeks thereafter depending upon whether their menstrual cycles are regular or irregular. To further control distribution, physicians must receive an authorization number that is placed on the prescription. Celgene also ships Thalomid directly to registered pharmacies and requires pharmacists to enter the authorization number for the prescription to receive confirmation to dispense the drug.

Since its inception, S.T.E.P.S. has successfully processed more than one million prescriptions (approximately 100 million thalidomide capsules) resulting in over 80,000 patient years of experience. Currently, there are more than 155,000 patients registered in the program as well as 36,000 pharmacies and 16,500 prescribers.

This track record contrasts with problems in the iPLEDGE™ restricted distribution program for isotretinoin, another teratogenic agent used to treat severe acne, which was instituted by the FDA in March 2006. The iPLEDGE program was a replacement for the failed SMART program (System to Manage Accutane Related Teratogenicity), originally implemented in 2002. In 2003, a first-year review of SMART compliance revealed that the number of pregnant women prescribed isotretinoin actually increased by hundreds of documented cases over the previous year.

Because SMART failed to manage risks effectively, the FDA required Roche Holding AG, the innovator company, and the three generic isotretinoin manufacturers to develop a stricter mandatory registry system that would document and verify all prescriptions written or dispensed to women of childbearing-age in the U.S. This led to the development of the iPLEDGE program. Specifically, iPLEDGE employs a Web site to register participating physicians, pharmacists and wholesale distributors and requires prescribers to register patients directly. Before starting isotretinoin, women must access iPLEDGE online or call a toll-free number to answer questions about program requirements and to verify the two types of contraceptives they are using. Women also must sign a document to acknowledge that isotretinoin can increase the

risk for birth defects, depression and suicidal thoughts.

From the FDA's standpoint, iPLEDGE is a significant improvement over the SMART program. But the program is far from error-proof. A 2007 assessment of the program's first year found that 122 women had become pregnant while participating in iPLEDGE, largely because they did not comply with their birth control regimens. Among manufacturers, program errors with iPLEDGE have raised concerns about liability issues if risk management systems are not rigorously administered. In June 2009, Hoffman-La Roche withdrew Accutane from the isotretinoin market, citing its business responsibilities in iPLEDGE as a major factor. Compounding the problem, in November 2008, a California Appellate Court ruled that Wyeth was liable for the harm caused to a patient taking a generic form of Wyeth's reflux drug Reglan, setting a precedent for shared liability in the future.

As the iPLEDGE demonstrates, designing and implementing an effective risk management system can be challenging, especially when the goal is zero tolerance. Thus, the working group applied lessons learned from the S.T.E.P.S. model to identify best practices for developing future restricted distribution plans. Specifically, the working group advocated an integrated system that:

- Builds on the ongoing collaboration between the manufacturer(s) and the FDA. In designing S.T.E.P.S., the agency and the manufacturer were equal partners in agreeing on the behaviors that could lead to fetal exposure and mapping out a step-by-step process to prevent these behaviors.
- Gives all stakeholders a seat at the table, taking into account the concerns and time-demands of pharmacists and physicians so the system will be clearly defined and not unduly burdensome.
- Integrates knowledge for the mutual benefit of all participants.
- Commits sufficient resources to educate and train prescribers and pharmacists and to provide counseling tools for patients.
- Develops clearly defined processes and procedures to address problems in real time.
- Establishes processes for taking corrective action, including re-education and training of physicians and pharmacies and removal of participants who fail to meet the program requirements.
- Designs systems to ensure confidential patient information is not distributed to third parties.

Another important take-away is the need for a significant investment in resources, both to design a rigorous risk management program and to operate the system on a daily basis. In the case of S.T.E.P.S., Celgene deploys more than 175 employees to monitor every aspect of the distribution of Thalomid capsules from manufacture to the patient. Having this direct control over access to thalidomide allows Celgene to track virtually every prescription. To summarize, a successful restricted distribution system requires that the sponsor take responsibility for design, management, and investment and establishes enforcement mechanisms to ensure compliance. There must be a well-defined chain of command. This commitment must be recognized by all concerned as a significant undertaking.

As the FDA begins to compel new restricted distribution programs under REMS, it is unclear

how the agency will apply these requirements to generic drugs. Generic companies must be required to marshal the necessary commitment to investment, management and responsibility because all manufacturers will have to be held to the same requirements for implementing a rigorous, strictly controlled system. As the case of isotretinoin makes clear, even when FDA deems the risk management plans as “equivalent and suitable,” implementation by different manufacturers can produce significantly different results. In particular, one isotretinoin manufacturer reported 18 pregnancies while another had none.

Unlike bioequivalence and other requirements for generic applications, FDA has not developed quantitative methods to evaluate or validate a generic’s risk management program. Nor has it developed a contemporaneous monitoring and enforcement policy. Since implementing restricted distribution systems requires a substantial investment in educating, training and monitoring physicians and pharmacies, the FDA must be able to assure that generic manufacturers have sufficient capacity and resources to safely and effectively administer a separate risk management program that is equivalent in rigor and scope to the existing system.

Ensuring the same degree of rigor also means addressing the outstanding issues regarding multiple risk management systems, especially where generic substitution is likely to occur. Because the experience with restricted distribution programs is limited, when there are multiple systems there must be assurance that each has the same ability to determine that the number of pills dispensed matches the authorized prescriptions.

3. Monitoring, Testing and Special Populations

Background Information

Phase I-III critical trials often under-represent certain groups, such as women, racial and ethnic minorities, and those living in rural areas. Without information on how a specific drug is metabolized in specific populations or in unidentified genetic subsets, unforeseen safety problems may appear after the drug is marketed, possibly resulting in increased morbidity or mortality for certain patients. For example, at the end of the 1990’s eight in ten of the prescription drugs pulled from the U.S. market were found to pose greater health risks for women than for men.

At the same time, the trend toward personalized medicine, which refers to the tailoring of medical treatment to the individual characteristics of different patients, implies a need for greater granularity of evidence of safety and efficacy. With the successful sequencing of a sample human genome, for example, it may become possible to document, describe, and profile the random pattern of human genetic variation and its link to disease risk in different patient groups. Findings from the large amount of genetic data generated to date show that more than 90 percent of the observed genetic variations occur within rather than between groups. These variations lead to major differences in how patients metabolize and react to different drugs. In fact, one study found that one particular cancer drug is ineffective in approximately 75 percent of patients. Greater understanding of differences in safety and efficacy across individuals could lead to enhanced care and an improvement in public health.

Although FDAAA does not address genetics as a risk factor that REMS could address, if variations in genetics are recognized as a safety factor for some drugs, then we can anticipate that one day, special populations will be recognized by genetic tests. In this scenario the strategies employed for REMS to mitigate risk—through communications or restricted distribution—would be available for the agency.

With this possible future in mind, this group began its “appreciative inquiry” with the example of a large-scale trial where gene-testing was used to optimize dosing of the blood-thinner warfarin. One of the most widely prescribed drugs in the world, warfarin is challenging for doctors to prescribe because the ideal dosage for each person varies widely and is hard to predict; one person may need 10 times more than another. Getting the wrong amount of warfarin can be dangerous: if the dose is too high, patients can bleed profusely; if the dose is too low, they can develop life-threatening clots.

Before conducting the trial, researchers knew that two genes, CYP2C9 and VKORC1, which vary slightly among individuals, can influence warfarin’s effectiveness. However, scientists did not know whether information about these genes could improve optimal dosage prediction for a wide range of patients regardless of race, ethnicity, or other genetic differences. To investigate this issue, researchers from more than 20 teams in nine countries on four continents voluntarily joined to form the International Warfarin Pharmacogenetics Consortium (IWPC), spearheaded by scientists involved in the National Institutes of Health Pharmacogenetics Research Network. By pooling their data, the consortium members had access to demographic information on 5,700 patients taking warfarin, including their age, sex, ethnicity, CYP2C9 and VKORC1 variants, and initial, as well as optimized, warfarin dosages.

Using this detailed information, scientists were able to calculate warfarin dosages in three ways: one that relied on the standard, clinical information; one that included additional information about individual patient variation in CYP2C9 and VKORC1; and one that used a fixed dose per day. When the researchers checked how closely their computational predictions matched the actual, clinically-derived stable warfarin dosage for each patient, they found that the predictions of ideal dosages were most accurate when the genetic information was included, especially for patients at the low or high ends of the dosing range. This is meaningful because nearly half of those on warfarin are at the extremes of the range, and these patients are typically at the greatest risk for excessive bleeding or clotting.

To build on these findings, Mayo Clinic collaborated on a prospective trial to determine whether genotyping patients before prescribing warfarin improved patient care and resulted in fewer hospitalizations over a 12 month period. Conducted in 2006, the study showed that genotyping was highly sensitive, allowed physicians to quickly optimize each patient’s dosage of warfarin, and led to lower levels of hospitalization compared to non-genotyped control. In 2007, the FDA worked with the makers of warfarin drug products to modify the product label to indicate that a patient’s genetic makeup may affect how he or she responds to the drug.

To build on this success, the group suggested that stakeholders could use REMS to facilitate communication between prescribers, laboratories, and pharmacies, leading to patients receiving

the appropriate dosing level of a specific drug on a sustained basis. Moreover, the group recognized the potential to capture this information within a patient's electronic health record so that future prescriptions are tagged for dosage and shared among clinicians. For this to occur, however, the group noted the immediate need for an infrastructure to collect rigorous, interoperable outcomes data that identify and evaluate signals of risk and effectiveness.

Genetic testing also has important implications when evaluating the comparative effectiveness of two competing drugs, especially when a generic competes with a brand name drug or two or more generic drugs can be used for the same indication. Because biomarker-driven drug development is a relatively new research field, there has been very little clinical data proving the cost-effectiveness and clinical utility of pharmacogenomics products. Thus, Medco recently launched its Genetics for Generics project, which thus far has used genetic testing to study warfarin dosing, tamoxifen response, and which acute coronary syndrome patients are most likely to benefit from the generic blood-thinner clopidogrel.

Applying this information through appreciative inquiry, the working group focused on those populations where monitoring programs under REMS have the greatest potential to improve clinical outcomes. They determined that monitoring has the greatest promise in patient populations who are: prone to under- or over-respond to usual dosing regimens; least able to tolerate, recognize, or communicate drug effects; or intentionally or accidentally overdosed. This includes patients at the extremes of age, adolescents, and patients who are taking multiple drugs.

Monitoring can also be an effective strategy for preventing dangerous under-dosing of patients, especially children who often require much more frequent doses, as well as greater doses per kilogram of body weight, to maintain therapeutic concentrations. Monitoring is also a useful tool for drugs that have no accepted standard "therapeutic ranges," such as many anticancer drugs.

Thus, FDAAA offers the FDA and the public health community new opportunities to collect data and information about drug use in specific populations. Towards this end, however, the working group called for upfront discussions between the FDA and other stakeholders, leading to consensus on those subpopulations and drug safety concerns where genetic testing and therapeutic drug monitoring offer the greatest opportunities to improve clinical outcomes. However, the group also advocated new policy to ensure that any new testing required under REMS will be reimbursed by private insurers and by the Medicare and Medicaid programs.

4. Product Quality Safety Studies

FDAAA directed FDA to create a new post-marketing surveillance system by 2012. This system, called the Sentinel System, will help the agency gather medical information by posing targeted queries (consistent with all applicable privacy and security safeguards) of electronic medical records, patient registry data, insurance claims data, and other large healthcare information databases. This new tool is designed to strengthen the agency's ability to track how drugs and other medical products perform once they go on the market and ultimately to communicate safety information to the public. The Sentinel System can make it possible to

detect rare but serious adverse events at an early stage, to provide early warning of a change in quality, and to identify hard-to-find product exposures.

Although FDAAA does not address problems associated with product quality, the fourth working group explored how FDAAA could be applied in this area in the future. They began their “appreciative inquiry” with the highly publicized recall of contaminated heparin. Beginning in January 2008, Baxter Healthcare Corporation recalled various lots of heparin, following a spike in reports of adverse events, including more than 80 deaths. This sparked an investigation by the FDA, which identified the cause: the anticoagulant was contaminated with over-sulfated chondroitin sulfate (OSCS), a compound derived from animal cartilage that mimics heparin and therefore was not detected in routine testing. Moreover, the FDA traced OSCS to 12 different Chinese companies and found the contaminant in batches shipped to 11 other countries. According to reports, in some samples of Baxter’s active ingredient, the contaminant made up between two percent and 50 percent of the total material.

From the perspective of risk mitigation, the FDA’s response to adulterated heparin demonstrates how the Sentinel System could be applied to address the quality of medical products in the future. In the case of heparin, the FDA was able to work with the U.S. manufacturer and experts in academia and private laboratories to carry out a thorough chemical analysis of the suspect products, using state-of-the-art technologies such as nuclear magnetic resonance, capillary electrophoresis, enzymatic kinetics, and bioassays to develop two new test methods that identified the contaminant. The agency then posted information on the two FDA-developed tests, recommended use of the tests to manufacturers and suppliers for screening heparin, and publicized its findings in two journal articles published on-line in the *New England Journal of Medicine* and *Nature Biotechnology*.

While the testing was underway, the FDA also issued a public health advisory to inform the medical community and the public about reports of serious adverse events in patients who received heparin manufactured by Baxter, and to recommend measures to minimize the risks in patients needing this therapy. Further, the FDA announced that all heparin coming into the U.S. from China was subject to an Import Alert, which gave the agency the authority to require that all shipments of heparin from China be sampled and tested before they could be used or sold in the U.S. During the recall, the FDA also worked with another U.S.-based heparin API manufacturer, APP Pharmaceuticals, to assure healthcare professionals and patients that there would be no shortages of this critical drug. Thus, in this example, the FDA was able to marshal existing resources and authority but was also required to obtain the voluntary cooperation of industry to control the situation.

Because the FDA will increasingly face challenges due to the globalization of drug development and manufacturing, the working group identified the potential for REMS and the new Sentinel System to allow FDA to prevent or rapidly detect drugs that may be contaminated in the future and to rapidly implement risk communications strategies to communicate safety information to the public in a crisis. Thus, the group called for an integration of the two initiatives so that they work in tandem. The group also recognized the ability of FDA to use new tools now available through REMS to provide better assurance of compliance with manufacturing controls. Pointing to the April 2008 recall of 800 million Digitek (digoxin) tablets that contained twice the

approved dose of the drug, the group said the agency already has broad discretion under REMS to require systematic post-marketing testing when FDA's Adverse Event Reporting System (AERS) receives reports linked to a class of drugs. In the Digitek case, between April and September 2009 AERS received reports of 2,912 serious injuries and 1,094 deaths associated with digoxin, with about 80 percent linked to Digitek.

Further, the group encouraged the FDA to apply the lessons learned from existing systems, such as RADAR (Research on Adverse Drug events And Reports), where investigators use hypothesis-driven active surveillance of a few hundred safety reports as the underlying conceptual framework to identify, clarify and verify serious adverse drug reactions and to report relevant ADR information. In some instances, investigators identify initial cases at hospital case conferences and report them to FDA or the pharmaceutical manufacturer. The RADAR methodology relies on initial recognition of these "sentinel" cases to identify quickly whether an unrecognized adverse drug event signal is present in the population of those exposed to a specific drug. REMS will then permit rapid development of requirements for further investigation or risk communication.

The Optimal Future for REMS: An Agenda for Action

Four Priority Areas for Action

The Food and Drug Administration Amendments Act (FDAAA) offers FDA a significant opportunity to use its new tools to reduce patient risks associated with medicine use. Before a new drug or biologic comes to market, FDA now has increased powers to require risk evaluation and mitigation strategies (REMS) as a condition of approval. The agency also has broad discretion to require REMS throughout the product lifecycle, mandate post-marketing restricted distribution systems for medicines that come with very high risks, and require post-approval studies and specialized labeling when the agency learns of a new serious risk associated with an approved product. Moreover, FDA can now harness scientific tools such as genetic testing and bioinformatics to identify drug treatments tailored to the needs of each patient.

Since March 2008, when the REMS provisions under FDAAA went into effect, FDA has already required a significant number of REMS, including signaling the agency's intention to require a class-wide REMS for opioid products. But to date, FDA policy on REMS has been implemented on a case-by-case basis. Further, the agency's draft guidance on REMS, issued in September 2009, perpetuates the approach of initiating and developing REMS solely as an interaction between the sponsor and FDA. Thus, a number of important challenges remain unaddressed, such as the linking of REMS to other healthcare system changes; linking REMS to electronic medical records; interaction with Medicare, Medicaid and health insurance entities; aligning REMS with FDA's new Sentinel Initiative; utilizing new knowledge gained from biomarkers to enable more effective interventions; developing uniform standards to assure that all manufacturers are held to the same requirements when implementing tightly controlled restricted distribution programs; involving patient advocacy groups, prescribers and pharmacists; and utilizing REMS as a tool to screen and evaluate drugs manufactured outside the U.S. or containing active ingredients imported from foreign countries. In short, the potential of REMS

and FDAAA compels us to apply a systems perspective that integrates all of these aspects.

To create the optimal future for REMS, workshop participants identified actions needed in the following areas:

1. Develop standard requirements, tools and protocols for designing and implementing REMS programs.

Because REMS represents a fundamental shift in learning about drug safety, implementing effective REMS programs requires that FDA:

- Create standards for REMS that anticipate the widespread adoption of electronic medical records (EMRs) and personal health records (PHRs) so that these systems are interoperable with REMS and so that EMRs and PHRs become enablers, not barriers, to post-market learning.
- Issue new guidance for designing post-marketing studies that includes demonstrated methods and measures to assess differences in sex, education and health literacy.
- Ensure uniformity and fairness so that both innovator and generic manufacturers are operating under the same requirements when designing, conducting and reporting the results of post-approval studies and implementing a communications plan.
- Consider FDA funding for communication plans that are imposed when the market is genericized and FDA bears the legal responsibility for developing and implementing a new communication plan.
- Ensure that all stakeholders are involved in the development of standardized REMS tools and the thresholds for imposition of the various REMS requirements.

2. Implement new policies to improve the administration of restricted distribution systems intended to prevent drug diversion.

Because significant program errors and lack of inspection and enforcement measures have been associated with some of the failures in restricted distribution systems implemented to date, new policies are needed to ensure that the goal of restricted distribution programs is met to stop drug diversion. Accordingly, the group recommends that the FDA:

- Standardize the procedures and controls whereby the agency works with the manufacturer to agree on the behaviors that could lead to a harmful exposure and the specific restrictions needed to prevent these behaviors.
- Develop quantitative measures to evaluate or validate each risk management program, including methods to determine in advance whether the sponsoring company has the capacity and resources to educate, train and monitor physicians and pharmacies.
- Ensure that all manufacturers – innovator companies and generic manufacturers – are held to the same requirements for implementing strictly controlled restricted distribution systems and that each such program has clear lines of control, investment and assignments of legal responsibilities.
- Implement measurable standards to ensure that when the brand name drug goes off patent and one or more generic versions enter the market, each risk management program is equivalent in rigor, investment, responsibility and scope as the original program.
- Establish requirements that ensure confidential patient information is not distributed to third parties.
- Coordinate with the states to ensure drugs dispensed under a restricted distribution

3. Utilize REMS to increase customized assessments of risks and benefits in special populations.

With the successful sequencing of a sample human genome, it will soon be possible to document, describe and profile the random pattern of human genetic variation and its link to disease in different patient groups. Therefore, the group recognized the potential for utilizing REMS to assess variations in risk and efficacy related to differences in age, sex, race, weight, diet, medical history, genetics, and other factors. Towards this end, the group called on the FDA to:

- Gain consensus on those special populations where monitoring programs under REMS have the greatest potential to improve clinical outcomes. These are likely to include patients at the extremes of age; adolescents; patients taking multiple drugs; and patients with variation in genes for drug metabolism (e.g., CYP), membrane channels (e.g., K⁺) or tumor markers (e.g., EGFR).
- Standardize the criteria for when the FDA will require genetic testing and other types of molecular medicine to identify the appropriate patients to receive a specific drug and the appropriate dosing level.
- Develop the technology and infrastructure so that there will be no barriers to collecting rigorous, interoperable outcomes data from EMRs and PHRs.
- Ensure that any new testing required under REMS will be reimbursed by private insurers and Medicare and Medicaid programs.

4. Apply new tools now available through REMS to assure the safety of the supply chain for medicines sold in the U.S.

At a time when more than 80 percent of the bulk substances used in drugs dispensed in the U.S. come from foreign sources, the FDA faces significant challenges in ensuring the safety and quality of the drug supply. Thus, even though REMS was not specifically designed for this purpose, the group believes that the new tools available through REMS could allow the FDA to provide better assurance of compliance with manufacturing controls. Towards this end, the group recommended that the FDA:

- Require systematic post-marketing testing when its Adverse Event Reporting System (AERS) receives reports linked to a class of drugs.
- Apply the lessons learned from existing adverse event reporting systems when utilizing REMS to identify drugs where manufacturing problems lead to serious safety problems. One such system is RADAR (Research on Adverse Drug events And Reports), which relies on a few hundred “sentinel” safety reports to identify quickly whether an unrecognized adverse drug event signal is present in the population of those exposed to a specific drug.
- Develop best practices for assuring the safety of the drug supply chain based on lessons learned from the recall of contaminated heparin where the agency used state-of-the-art technologies to identify the contaminant, developed new test methods so manufacturers and suppliers could screen patients, and informed the medical community about measures to minimize risks in patients needing the therapy.

- Integrate REMS with ongoing planning for the implementation in 2012 of the new Sentinel System so that the two initiatives will work in tandem. The new Sentinel System will track how drugs perform once they go on the market through information gathered from electronic medical records, patient registry data, insurance claims data and other large health care information databases.
- Also, the group recommended that Congress pass the *FDA Globalization Act*, which would give FDA more resources to inspect all foreign manufacturing sites that export medicine and drug ingredients to the U.S. and to oversee the safety and quality of generic drugs manufactured by foreign companies.

The Time is Now!

Creating a public policy agenda that charts a path towards the optimal future of REMS is essential to improving safe drug use. However, REMS will not be successful unless there is a coordinated approach to systems change. REMS must be incorporated into the workflow of physicians and pharmacists and integrated with all records and pharmacy management systems. A coordinated approach to systems change is vital when REMS impose procedures or testing that should be reimbursed and impact patients' access to effective drugs.

Everyone in the health care system has a significant role to play in ensuring that REMS fulfills its potential and benefits all involved. The policies that are put into place under REMS will affect every stakeholder, especially the patient. With this in mind, the proposed action agenda described above develops a common framework for REMS that takes into account lessons learned from front-line experiences with existing risk management programs to allow for the maximization of benefits to all stakeholders with patients as the center of concern. The agenda also factors in recent technological advances that are changing the way medicine is practiced. Clearly, the time for action is now to develop an optimal future for REMS.



Appendix A: Workshop Participants

Group 1 – Post Approval Studies/Special Labeling Communications

- Kimberly Thompson, ScD, M.A. – Associate Professor of Risk Analysis and Decision Science, Harvard School of Public Health
- Susan Berger, PhD - Senior Director, Risk Management Strategy, Safety and Risk Management, Pfizer
- Theresa Mullin, PhD – Associate Director for Planning and Informatics, FDA CDER
- Terri Madison, PhD, MPH – President of i3 Drug Safety
- Patrick Brady, Pharm.D. – Manager, Office of Scientific & Regulatory Affairs, Eli Lilly & Co.
- Jane Reece-Coulbourne – Chairman of the Board, Lung Cancer Alliance

Group 2 – Restricted Distribution

- Phyllis Greenberger, MSW -- President and CEO, Society for Women’s Health Research
- Suzanne Barone, PhD – Office of Compliance, FDA CDER
- Jur Strobos, MD, J.D. – Of Counsel, Olsson Frank Weeda Terman Bode Matz, PC
- Marcie Bough, PharmD. -- Director of Federal Regulatory Affairs, American Pharmacists Association
- John Chin – Executive Director of US Marketing & Marketing Operations, Celgene Corporation
- Brenda Wright – Vice President, Marketing and Business Development, Proherant
- Florence Houn, MD – Vice President of Regulatory Policy and Strategy for Regulatory Affairs, Celgene Corporation

Group 3 – Monitoring, Testing, or Special Populations

- Martha Nolan, J.D. – Vice President for Public Policy, Society for Women’s Health Research
- Jeff Allen, PhD – Executive Director, Friends of Cancer Research
- Diane Dorman PhD – Vice President for Public Policy, National Organization for Rare Disorders; Board of Directors, Alliance for a Strong FDA
- Felix Frueh, PhD – Vice President of Personalized Medicine Research & Development, Medco Health Solutions, Inc.
- Edgar Gil – Health Program Manager at National Alliance for Hispanic Health

Group 4 –Product Quality Safety Studies

- Sally Greenberg, J.D. -- Executive Director, National Consumers League; member of FDA Risk Communication Advisory Committee
- Mary Pendergast, J.D. – President, Pendergast Consulting
- Michael Wolf, PhD, MPH. -- Associate Professor, Medicine and Learning Sciences and Associate Division Chief of Research, Division of General Internal Medicine, Feinberg School of Medicine, Northwestern University
- Kathleen Frost – Associate Director for Regulatory Policy, Office of Surveillance and Epidemiology, FDA CDER

- Claudia Karwoski, PharmD – Division Director, Division of Risk Management, Office of Surveillance and Epidemiology, FDA CDER
- Alan Levine – Chair for Public Policy, Consumers Advancing Patient Safety (CAPS)
- Rebecca Noel, DrPH, MSPH –Research Scientist, Office of Risk Management and Pharmacoepidemiology Eli Lilly and Company



Appendix B: Background Information for REMS Groups

Group 1 – Post Approval Studies/Special Labeling Communications

Post-approval studies have been one mechanism used to confirm efficacy but have also been required to evaluate safety 'signals.' Post-approval studies could be controlled, observational or epidemiological, such as healthcare database analyses. Another method of assuring safe use have been requirements for communication plans, including Black Box Warnings, MedGuides, Patient Package Inserts, mandated pharmacist-patient consultations, various forms of Dear Doctor letters, and public health advisories. These have mostly been applied on approval. New legislation permits imposition of a post-approval study requirement and also communication plans following identification of a new serious safety risk. Since the market has moved to generic dominance, how will such post-marketing controls be applied to both branded and generic compounds?

Group 2 – Restricted Distribution

When it comes to drug safety, certain drugs present a dilemma: They can provide an important benefit to patients, but these compounds can be especially dangerous if not used properly. For example, certain drugs may be safe and effective for patients, but if taken while pregnant can harm the fetus or cause miscarriage. Rather than deny approval of such drugs, FDA may require the manufacturer to develop a restricted distribution plan to ensure that the drug is distributed under tightly controlled positions. This may require a closed-loop performance-linked access system, such as the System for Thalidomide Education and Prescribing Safety (“S.T.E.P.S.®”) developed to control the distribution of thalidomide. Such restricted distribution programs may necessitate physician qualification and registration, patient informed consent, and pharmacist distribution limitations as well as ongoing systems to track every aspect of the drug’s distribution. Additionally, restricted distribution may include warnings or precautions relative to a specific subpopulation or require post-approval studies in such a population. Thus, restricted distribution systems can be costly to develop, implement and manage and require an ongoing investment of trained personnel and the infrastructure to assure drug safety.

Group 3 – Monitoring, Testing, or Special Populations

Increasingly safety risks can be limited by certain special monitoring or screening to assure that complications are identified early and drugs are prescribed as labeled. Studies on differences in individual metabolism or genetics suggest that further such controls may be imposed, for instance, requirements for assessment of KRAS mutation in the use of cetuximab and panitumab. Concomitantly, Congress is considering health care reform. The likelihood is that new controls will be implemented to assure safe and appropriate use of pharmaceuticals. How can these controls be dove-tailed with requirements set forth by FDA for safe use of pharmaceuticals?

Group 4 –Product Quality Safety Studies

Frequently, post-approval requirements have included nonclinical studies addressing the quality of medical products: including changes to manufacturing, evaluations of alternative

manufacturing procedures, methods or product testing. Recent concerns have been raised about manufacturing fraud in products manufactured overseas. Advances in chemistry or biotechnology may raise issues with regard to historic production techniques, such as the new discovery of new or rare organisms that may contaminate fermentation systems or differences in manufacturing may result in immunological differences. How can FDA provide better assurance that there is compliance with manufacturing controls especially given changes in manufacturing sites, increasing generic dominance, and the need for cost savings?