



REMS Compliance

Review of US REMS Regulation and Compliance

Jean Steckler, Senior Vice President

June 2010

Table of Contents

I	Executive Summary.....	3
II	Background	4
	A. Legal Requirements	4
	B. Accountability	4
	C. Health Care Provider (HCP) Needs.....	5
III	REMS Programs.....	6
	A. Requirements.....	6
	B. Industry Response.....	6
	Cephalon	6
	Amgen	6
	C. Elements to Assure Safe Use (ETASU).....	7
	Gilead	7
IV	Evolving Safety Regulations and Risk Management Programs.....	9
	A. Roche/Genentech – Accutane Risk Management	9
	B. Amgen (ESA Class REMS)	11
	Physician Tracking	11
	Hospital Tracking.....	11
	Pharmacy Tracking.....	11
	APPRISE Website.....	12
VII	Current Trends	12
VII	The Missing Link.....	12
IX	Best Practices and Recommendations.....	13
	APPENDIX A REMS Requirements.....	16
	APPENDIX B FDA Evolution of Risk Management Regulations And Pharmaceutical Risk Programs	18
	APPENDIX C New 2010 REMS Programs	20
	APPENDIX D Modified 2010 REMS Programs	21
	End Notes.....	22

Risk Mitigation Regulation and Compliance Review

I Executive Summary

FDA regulations regarding risk management have been growing since Thalidomide was found to cause birth defects. The passage of the Food and Drug Administration Amendments Act of 2007 (FDAAA) mandated enforceable guidelines referred to as Risk Evaluation and Mitigation Strategies (REMS).

Designed and implemented properly, a REMS program both protects patients from known or potential serious risks, and offers an economic upside to the biopharmaceutical business.

Several REMS components include commonly used communications tools, such as Patient Package Inserts (PPI), Medication Guides, and Dear Doctor/Dear Pharmacist letters. Other elements may also include HCP (Health Care Providers) and pharmacist education, restrictive distribution, dispenser and patient registries, and required patient laboratory testing.

To maximize patient benefit as well as HCP and pharmacy efficiencies, automation within and across systems is required. For more complex REMS systems, automation will improve patient, HCP and pharmacy compliance. Examples include:

- Automated IVR, email, SMS reminders to patients to remind them of upcoming laboratory testing and refill dates
- Automated alerts to HCP and pharmacies when patients report that they will not comply with laboratory testing or refill pick ups
- Automated distribution and printing of Medication Guides at the pharmacy and HCP office
- Online access for:
 - pharmacies to determine certification status of HCPs
 - prescribers to determine certification status of pharmacies
 - wholesalers to determine certification status of pharmacies
 - HCP and pharmacy training and certification
- Online storage of HCP and Patient Agreement documentation

Much of current record keeping is paper-based, providing gross inefficiencies and poor transparency for all stakeholders. These problems will be resolved as the FDA approves previously paper-based REMS processes.

II Background

The U.S. healthcare system is undergoing radical change. Small physician practices are rapidly being replaced by large corporate health care systems. Independent hospitals are merging into wider, regional health systems. The FDA is requiring greater communication among healthcare professionals, pharmacies and pharmaceutical manufacturers to protect patients from avoidable adverse events. For medications with known risk factors, the FDA requires manufactures to provide Risk Evaluation and Mitigation Strategies (REMS).

To better ensure proper drug use and to keep Health Care Providers (HCPs) and patients informed about the safety and efficacy of drugs, the REMS program was established as one of many post-marketing safety provisions included in the [Food and Drug Administration Amendments Act of 2007 \(FDAAA\)](#). This legislation increased the FDA's ability to require labeling changes, post-approval studies, and publication of clinical trial results.

Since the program went into effect in March 2008, the FDA has negotiated more than 100 REMS programs as part of the approval of new drugs.

The list of specific risk mitigation components that may be required is provided in Appendix A.

A. Legal Requirements

Before the FDAAA was enacted, the FDA approved a small number of drug and biological products with risk minimization action plans (RiskMAPs) to reduce known risks while preserving drug benefits. As a result of the FDAAA, REMS programs are required for new drug applications (NDAs), abbreviated new drug applications (ANDAs), and biologics license applications (BLAs).

With REMS, healthcare providers (HCPs) and pharmacies have an additional set of responsibilities to their patients. REMS programs provide checklists, akin to those developed by Atul Gawande for surgery.¹ These FDA-mandated requirements are cross-functional checklists for health care providers (HCPs), pharmacies, patients, manufacturers and, in some cases, distributors.

The key to successful implementation is to make these cross-functional processes as simple and transparent as possible – employing automation and data storage – to minimize the burden of REMS programs on the entire healthcare system.

B. Accountability

The FDA places the responsibility for designing REMS programs on the pharmaceutical manufacturers, who are exposed to civil penalties for REMS non-compliance. Penalties include a maximum of \$250,000 per violation, not to exceed \$1 million. However, if the violation continues after written FDA notice, the manufacturer is fined \$250,000 for the first 30 days, doubling with each 30 day period, not to exceed \$1 million in a 30 day period and a maximum of \$10 million for all violations adjudicated in a single proceeding.

If a generic company manufactures a REMS-regulated product, the generic company is required to use a single shared system with the product innovator (NDA holder) or to obtain a waiver. In these cases, the innovator company is responsible by the FDA for negotiating with the generic company. The NDA holder is responsible for the REMS strategy, design and implementation – a difficult situation where they bear responsibility without authority over the companies that manufactures the generic drugs.

Pharmaceutical companies also need to earn the acceptance of the REMS program from HCPs, pharmacies, and distributors (when required). Since their customers' participation is optional, their level of participation can make or break the success of the brand. Manufacturers cannot make their customers participate, but they can work towards getting customers to want to participate. Their task is to understand what is important to these customers and offer the solutions to provide it.

A survey conducted by ParagonRx gives some insight into HCP acceptance of REMS programs. In this survey, clinicians who perceive the REMS program as beneficial or appropriate responded that the program would increase their intention to prescribe by as much as 42%. In contrast, among those who found the program to be burdensome or inappropriate, their intention to prescribe was reduced by as much as 58%.²

C. Health Care Provider (HCP) Needs

The HCPs' primary responsibilities to their patients are to evaluate, diagnose, consider treatment options, discuss, recommend and prescribe a treatment, and re-assess to continually improve health outcomes. Any aid that makes this process more efficient is welcome. In contrast, any task that interferes with the process drains resources.

Typical HCP offices are not designed to meet even the most basic REMS requirements. Rarely will a physician's office have a repository of literature and methods for easily and efficiently providing the appropriate literature to patients at the point of care. Nor do they have the administrative staff to order literature from each manufacturer when the HCP's supply runs out.

For more rigorous REMS programs, the challenges of keeping patients compliant exceed most HCP office technology. Even if a practice uses a telephone-based automated appointment reminder system, these systems do not provide patient feedback to all the stakeholders involved in the patient care -- the HCP, laboratory and pharmacy. As a result, they do not provide comprehensive patient care efficiently.

Fortunately good solutions are emerging to solve these problems. When HCPs can automatically print as well as email Medication Guides to patients, and automatically schedule appointment reminders for all required tests – HCPs can meet REMS obligations without burdening their office with excessive administrative work.

III REMS Programs

A. Requirements

The requirements of REMS programs vary by class or by specific drug. They may include Medication Guides, Patient Package Inserts (PPI) and Communication Plans. It may also include:

- Restricted refills dependent on the results of laboratory testing
- Patient registries
- Specialized training, and/or
- Certification for prescribers and pharmacists (see Appendix A).

B. Industry Response

The most rigorous REMS requirements to date are for long-acting and extended-release opioid drugs. For 24-hour, long-acting or extended-release opioid products, the FDA has asked manufacturers to develop a single REMS program for the drug class instead of separate programs for each product.³ The industry has responded by establishing an Industry Working Group (IWG) comprised of representatives from 22 pharmaceutical companies. This IWG provided a draft of its recommendations for a class-wide opioid REMS program in December 2009.⁴

Cephalon

While the IWG was preparing its response to the FDA, Cephalon sponsored an industry-wide online portal for REMS compliance for drugs treating pain at <http://www.readyforrems.com>. It should be noted that Cephalon's ACTIQ® (oral transmucosal fentanyl citrate) was the first FDA approved opioid with a Risk Management Plan in 1998. Cephalon has branded their Risk Evaluation and Mitigation Strategy (REMS) for FENTORA® (fentanyl buccal tablet) as COVERS™.

Amgen

In February 2010, the FDA announced a second REMS class-wide restriction for all Erythropoiesis-Stimulating Agents (ESAs), such as Procrit, Eopgen and Aranesp – all Amgen products.⁵ To comply, Amgen established an HCP registry called "Assisting Providers and Cancer Patients with Risk Information for the Safe use of ESAs (APPRISE)." (This program is described in more detail in Section VIII.)

The FDA is increasing the number of REMS drug classes. In February 2010, the FDA called for a class-wide REMS for long-acting asthma drugs. A broader REMS for ESAs in renal-disease treatment is under development. Additional initiatives may be launched for anti-seizure drugs and anti-depressants, as well as other medicines that carry risk. The industry anticipates that the FDA will require REMS for *most new* medications.

When a class-wide REMS program has not yet been developed, manufacturers are left to determine how to comply with REMS requirements on their own. Some REMS components such as Medication Guides,

PPIs and Communication Plans (such as “Dear Healthcare Provider” letters) are well understood and relatively easy to implement.

Other components, such as Elements to Assure Safe Use (ETASU), may require the brand to build new communication and feedback mechanisms between the HCP and the pharmacy. In these cases, manufacturers can improve their probability of launching a successful REMS program by adopting off-the-shelf solutions and thereby:

- Decreasing development time to implement
- Reducing risk for implementation
- Benefiting from economies of scale

C. Elements to Assure Safe Use (ETASU)

An ETASU may require that a drug be dispensed to patients with evidence of safe-use conditions. For example, certain patient laboratory test results may be required before a drug may be dispensed.

Currently the FDA requires 12 drugs to provide ETASU in their REMS program, four of which are in either ESA or Opioid classes.⁶ Table 1 lists these drugs, their REMS class, if any, the manufacturer and indications.

Gilead

By way of example, we provide a deeper look into the REMS ETASU requirements for LETAIRIS. Gilead’s extensive REMS program provides the goals, details and implementation plans for this drug.⁷

LETAIRIS’ REMS program strives to minimize the risk of hepatotoxicity and risk of fetal exposure. To minimize these risks, women who are pregnant cannot be prescribed LETAIRIS, and those who do take LETAIRIS must not become pregnant. Gilead’s ETASU program provides for a prescriber certification process, and prescriber attestations regarding patient communications (Medication Guide and Patient Educational Brochure). Prescribers also must agree to “order and review liver function tests (including aminotransferases and bilirubin) and pregnancy tests (for female patients of childbearing potential) prior to initiation of LETAIRIS treatment and monthly during treatment.” If the patient does not comply with these tests, the prescriber must counsel the patient.

Prescribers face a burdensome series of activities. They must prescribe the monthly tests, determine if the tests were completed satisfactorily, and counsel non-compliant patients – a recurring set of tasks that would be difficult for even the most efficient physician offices without the additional support of automated systems.

Gilead’s ETASU program also provides a certification process for all pharmacies, hospitals, HCP offices and other health care settings (e.g., clinics) that dispense LETAIRIS. Before dispensing this drug, the dispenser has to first receive acknowledgement of prescriber and patient enrollment, and HCP

attestation that they have counseled patients on risks and benefits. Refills are restricted to a 30-day schedule. Those who prescribe also are required to “speak with each patient, or their prescriber, every month to obtain confirmation that liver function testing and, for female patients of childbearing age, pregnancy testing was completed.”

As with HCPs, these recurring tasks are challenging for even the most efficient pharmacies, and they would benefit from automation.

Table 1: Drugs Required by FDA to Include REMS ETASU Component

Class	Manufacturer	Drug	Indication	REMS Program
ESA	Amgen	Aranesp (darbepoetin alfa) Injection	Anemia, chronic kidney failure, chronic renal failure, anemia from chemotherapy	APPRISE ⁸ esa-apprise.com
ESA	Amgen	Epogen/Procrit (epoetin alfa) Injection	Chronic kidney failure	APPRISE ⁹ esa-apprise.com
Opioid	Purdue Pharma L.P.	Oxycontin (oxycodone hydrochloride) Controlled-Release	Pain	www.oxycontinrems.com ¹⁰
Opioid	Mallinckrodt, Covidien company	Exalgo (hydromorphone hydrochloride) Extended-Release Tablets	Pain	Exalgo Alliance ¹¹
	Roche Covance	Accutane* (isotretinoin)	Acne	iPLEDGE ipledgeprogram.com
	Adolor & GSK	Entereg (alvimopan) Capsules	GI Recovery after bowel surgery	E.A.S.E. ¹² www.entereg.com/ease-program.html
	Gilead	Letairis(ambrisentan)	Pulmonary arterial hypertension	LEAP ¹³
	Amgen	Nplate (romiplostim)	ITP	NEXUS ¹⁴ Nplate.com
Opioid	Meda Pharmaceuticals	Onsolis (fentanyl buccal soluble film)	Break through pain in cancer	FOCUS ¹⁵

	GSK	Promacta (eltrombopag) Tablets	Thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.	Promacta Cares ¹⁶ www.promactacares.com
	Lundbeck Inc.	Sabril (vigabatrin) Tablets and Oral Solution	Infantile spasms (IS)	S.H.A.R.E. ¹⁷ www.lundbeckshare.com
	QOL Medical	Sucraid (sacrosidase) Oral Solution	Congenital sucrase-isomaltase disease (CSID)	Sucraid REMS ¹⁸
	Actelion	Tracleer (bosentan) Tablets	Pulmonary arterial hypertension (PAH) WHO Class II-IV	Tracleer Access Program [T.A.P] ¹⁹
	Eli Lilly	Zyprexa Relprevv (olanzapine) Extended-Release Injection ¹²⁵	Bipolar I Disorder Schizophrenia	ZYPREXA RELPREVV Patient Care Program ²⁰

(*Included as part of the isotretinoin Risk Management Program. Manufacturers participating in the iPLEDGE program include: Roche Laboratories, the innovator company, and three generic firms—Genpharm, Ranbaxy Pharmaceuticals, and Barr Laboratories.)

IV Evolving Safety Regulations and Risk Management Programs

REMS requirements for a drug or drug class are continuously evolving. The FDA solicits feedback and collaborates with pharmaceutical companies in an effort to find the right balance between patient risks and benefits. Much of the REMS design has evolved from earlier work on Risk Management Programs and RiskMAPs. A detailed timetable of regulations and risk programs can be found in Appendix B.

A. Roche/Genentech – Accutane Risk Management

Roche and Genentech (recently acquired by Roche), have had extensive experience with the FDA's changing risk management requirements. Nine Roche medicines have risk programs with mature drugs, across several therapeutic areas. Two of these products, Accutane® for acne and Cellcept® for transplants, require ETASU, Registries, and Implementation Systems, in addition to Medication Guides and Communication Plans, in an effort to avoid birth defects.

Roche launched its first voluntary Accutane Risk Management Program in May 1988, called Pregnancy Prevention Program (PPP). The PPP was a voluntary program for both the prescriber and patient. Its

second program, System to Manage Accutane Related Teratogenicity (SMART) was launched in April 2000 in response to new FDA restrictions. It required mandatory participation by both the prescriber and female patients.

In February 2002, Roche's patents for isotretinoin expired and there are now many other companies selling less expensive generic versions of the drug. Once generic manufacturers entered the market, risk management was no longer centralized.

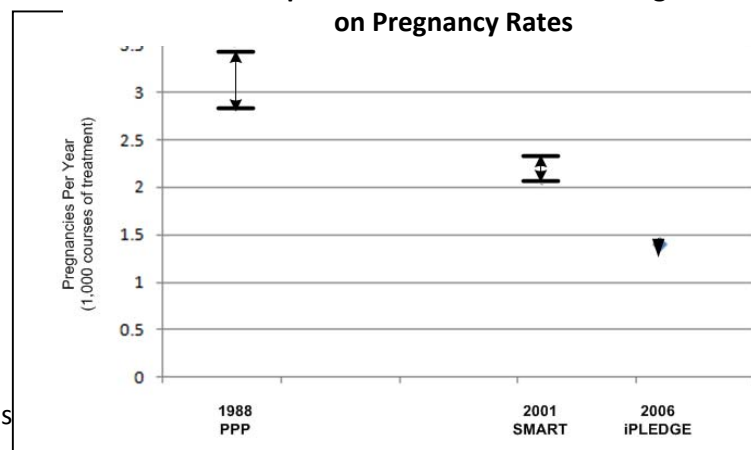
Since March 2006, the dispensing of isotretinoin in the United States has been controlled by an FDA-mandated website called iPLEDGE, which requires dermatologists to register their patients before prescribing the medication. Pharmacists are required to check the website or call a call center to determine if the patient has registered before dispensing the drug. Additionally, doctors and pharmacists must verify written prescriptions in the iPLEDGE system before patients may fill the prescription. And, women must be on a form of birth control.²¹ The prescription may not be dispensed until both parties have complied.

On June 29, 2009 Roche Pharmaceuticals, the original creator and distributor of isotretinoin, officially discontinued both the manufacture and distribution of their Accutane brand in the United States. Generic isotretinoin remains available in the United States through Teva, Ranbaxy and Mylan.

Since the iPLEDGE program pre-dates REMS, which assigns responsibility for the REMS program to the NDA holder, iPLEDGE was and continues to be sponsored by all isotretinoin manufacturers. It is a mandatory program for prescribers, all patients (male and female), dispensers and wholesalers. IPLEDGE is a technology-based system, using both a phone and a web interface (www.ipledgeprogram.com) that tracks all registrations. ETASU requires a monthly pregnancy test by a CLIA-certified lab, and results need to be entered into the iPLEDGE system before a script can be filled. Components include:

- Applications Development and Hosting
- Adverse Event Management
- Data Analysis and Reporting
- Document production and fulfillment
- Patient surveys via web and IVR
- Call Center Management
- Pregnancy Registry
- Education Materials Design & Update
- Assessments
- Performance-Linked Access System requiring pregnancy test results and contraception choices

Chart 1 Impact of Isotretinoin Risk Management on Pregnancy Rates



As can be seen in Chart 1, each new risk management program decreased the frequencies of pregnancy while patients were treated with isotretinoin. With the PPP program, there were 2.8 to 3.4 pregnancies per 1,000 courses of treatment. The SMART program resulted in 2.1 to 2.3 pregnancies per 1,000 courses of treatment. And iPLEDGE produced the least number of pregnancies, 1.3 pregnancies per 1,000 female users of the program.^{22 23}

B. Amgen (ESA Class REMS)

In 2008, the FDA required Amgen to provide an ESA class-wide REMS program for cancer patients. Amgen is currently the sole manufacturer of FDA-approved ESAs, and Centocor Ortho Biotech is a marketing and distribution partner on Procrit. The risks to be managed were based on studies that found ESAs caused tumors to grow faster and resulted in earlier deaths in certain cancer patients.

To meet the FDA requirements, Amgen developed a program called APPRISE (Assisting Providers and Cancer Patients with Risk Information for the Safe Use of ESAs).

The program includes the following components.

Physician Tracking

- Physician registrations faxed or mailed to a third-party call center that oversees and monitors compliance
- Documentation of HCP's completion of training on ESA usage
- Discussion of the risks, benefits and approved usage of ESAs with each patient before they begin treatment
- Written acknowledgment from both the doctor and patient that the discussion took place, which are faxed or mailed to the third-party call center.
- Re-enrollment in the program every three years.

Hospital Tracking

- Dispensing hospitals designate who "assumes the authority and responsibility" to internally coordinate and oversee the institution's program (often the pharmacy manager)
- Documentation of hospital's designee's completion of training module
- Compilation of lists of everyone at the hospital who prescribes ESAs to cancer patients
- Proof that each one has enrolled in APPRISE
- Archive of the written acknowledgments from every cancer patient who receives ESAs

Pharmacy Tracking

- Validating the prescriber is an approved APPRISE registrant
- Receipt of acknowledgement of patient discussion with signatures from HCPs and patients.

APPRISE Website

The APPRISE website, www.esa-apprise.com, provides online access to physicians and hospitals to the following literature and forms:

Physicians

- PPIs
- Medication Guides
- Dear Healthcare Provider (DHCP) Letters to HCPs
- REMS Flashcard (Prescriber checklists)
- Provider Flashcards (Prescriber process flowchart)
- HCP Training Module
- HCP Enrollment Form
- Patient and Healthcare Professional (HCP) Acknowledgment Form

Hospitals

- Dear Healthcare Provider (DHCP) Letter to Hospital Directors of Pharmacy/Administrators
- Hospital Process Overview
- Hospital Designees Training Module
- Hospital Enrollment Form

Patients

- Patient Instructions for Use (for self-administration)

VII Current Trends

On-demand printing of Medication Guides and Patient Package Inserts (PPI) has become part of standard pharmacy operating procedures with systems such as LDM Group's CarePoints® and Catalina's PatientLink®. HCP on-demand printing is gaining acceptance with systems such as LDM Group's ScriptGuide®.

Also, systems for reporting adverse events have a long-established track record, with available solutions such as the FDA's MedWatch website, the Relsys Argus Safety data management and regulatory reporting system, Oracle AERS, and others.

VII The Missing Link

The missing link in REMS ETASU programs is the feedback loop among the prescriber, the lab (when required), and the pharmacy, which is still paper-based, taxing HCPs and pharmacies with overly

burdensome administrative processes. Fortunately, technologies such as iReminder's **MedTrigger**SM can automate communications among these stakeholders.

Help Patients Comply with Scheduled Tests

Patients need to complete lab tests in a timely basis to avoid lapses in their prescription refills. To help patients stay on schedule, **MedTrigger** schedules automated reminders. Reminders are scheduled to be delivered to patients prior to their anticipated lab dates (e.g. two weeks, one week and two days before) and to confirm that patients will keep their scheduled appointment. When patients report they will not go, **MedTrigger** automatically generates alerts to the HCP and the pharmacy.

To accommodate different patient lifestyles, **MedTrigger** contacts the patient according to their preferred method of communication (email, phone, SMS text, iPhone app). If a patient is not reached at one destination, the system escalates to the patient's next preferred location. Furthermore, multiple attempts are made at each location until the patient has been reached. This technology ensures that every effort is made to reach the patient.

IX Best Practices and Recommendations

We propose a list of best practices and recommendations for implementing REMS. These programs are still in their infancy and we see opportunities to create effective programs that will benefit all stakeholders.

Facilitate Communications

While elements may differ, the foundation of a REMS program is communications among health care providers, pharmacists and patients, as mandated by the FDA. Currently, most of these communications are pre-printed and paper-based. Furthermore, HCPs and pharmacists have to deal with multiple suppliers rather than single electronic source for generating print materials. Even worse, when documents are revised, their distribution is slow.

We recommend automating these communications whenever possible, replacing them with online systems to improve efficiencies and reduce administrative work for all parties. The benefits include:

- There will be a single electronic source for generating documents that must be printed
- Adequate documents will always be available
- Storage and retrieval of documents will be efficient
- Compliance levels will increase

Improve Patient, HCP and Pharmacy Compliance

Compliance levels with REMS programs are low because they interrupt the workflow²⁴ of HCPs and pharmacists and because implementing the elements is a manual process²⁵. Even the most efficient HCP offices and pharmacies find that adhering to these programs are challenging. They would, therefore, benefit greatly from automation. Examples include:

- IVR, email and SMS text reminders to patients to remind them of upcoming laboratory testing and refill dates
- Alerts to HCP and pharmacies when patients report that they will not comply with laboratory testing or refill pick ups
- Distribution and printing of Medication Guides at the pharmacy and HCP office

They also would benefit from online access for:

- Pharmacies to determine certification status of HCPs
- Prescribers and wholesalers to determine certification status of pharmacies
- HCP and pharmacist training and certification
- Storage of HCP and Patient Agreement documents

Integrate REMS Program with Pharmacy Management Systems and HCP Systems

The FDA requirement that Medication Guides be printable from PDF formats has slowed the adoption of electronic Medication Guides in mainstream pharmacy practice management systems. However, new solutions, such as on-demand printing of Medication Guides, are being integrated into systems such as QS/1 and SpeedScript using LDM's CarePoints®. Similar on-demand printing for HCPs office is beginning to emerge as well.

Prepare for the growth of the generic drugs market

When new drug applications (NDAs) are filed with the FDA, the REMS accountability remains with the NDA holder who takes the lead in coordination among all new sponsors. Therefore, pharmaceutical sponsors facing generic competition at some point in their life cycle should automate for efficiency to reduce their work load when abbreviated new drug applications (ANDAs) are approved down the road.

We recommend that NDA holders draft a Memorandum of Understanding (MOA) for all ANDAs and sponsors to sign, which contain:

- Rules of engagement
- Ownership rights of intellectual properties
- Cost sharing structure
- Contracts regarding cost sharing and third-party call centers
- Share of voice and escalation process²⁶

- The roles and responsibilities of each company's program manager
- Governance (how program is governed among multiple partners)
- Exit Strategy

Following the model established by Roche, we recommend that NDA and ANDA holders share REMS program development costs. Ongoing maintenance costs should be adjusted based on relative market share.

Furthermore, efficiencies are extremely critical when generic sponsors join the REMS program, since they do not have the same depth of relationships with stakeholders, nor do they have comparable internal infrastructure systems.

Automate Reporting Systems

Every REMS program includes an assessment timeline that typically involves a public review of the program's impact at 18 months or after 10,000 patient exposures. Under FDAAA, the agency is required to "prepare...a summary analysis of the adverse drug reaction reports received for the drug, including identification of any new risks not previously identified, potential new risks, or known risks reported in an unusual number." Improved automation will provide the metrics and reporting necessary to evaluate and continuously advance REMS programs.

Standardize Requirements

The key to success of REMS programs is standardized requirements and uniform methods in design and implementation. Even more important is to link REMS to electronic medical records, health plans, and to other adverse event programs, so that the healthcare system will have the information it needs to effectively treat diverse patient populations.

APPENDIX A

REMS Requirements

The FDA can require specific levels of risk mitigation, depending on the drug's risk and adverse effects. The six levels of risk mitigation are listed below, followed by an explanation of the requirements of each.

1. Professional Label and Package Insert
2. REMS – Medication Guide
3. REMS – Communication Plan
4. REMS – Elements to Assure Safe Use (ETASU)
 - With Registry
 - Without Registry
5. Implementation System
6. Timetable for Assessment

Medication Guide/Patient Package Insert (PPI) (Regulation 505-1(e))

The Medication Guide and PPI are education tools provided to each patient when the drug is prescribed/dispensed.

Communication Plans (505-1 (e))

Communication Plans discuss the key patient monitoring protocols and serious adverse events and often include the techniques required to safely administer the medication to the patient. Communication Plans may include:

- Letters to healthcare providers
- Communications to professional societies
- Professional education
- Black box warnings
- FDA talk paper
- Information on the FDA website

Elements to Assure Safe Use (ETASU) (505-1(f) (3))

ETASU places special requirements or restrictions to optimize safe use of products. The FDA intends through the use of ETASU and PLAS (performance linked access system) to drive performance and specific activities between healthcare practitioner and patient that can serve to reduce their risk profile. Tools can include training videos, protocols, laboratory monitoring schedules, sample informed consent agreements between patient and healthcare practitioner, and other data collection tools. REMS ETASU drugs often require the patient, HCP, pharmacy and distributor to link their performances to maintain safe drug use.

ETASU may include the following elements:

- Prescribers have certain training or certification
- Facilities dispensing the drug are certified
- Drug is only dispensed to patients in certain settings (e.g., hospitals)
- Drug is dispensed with documentation of safe-use conditions (e.g., laboratory tests)
- Patients be subjected to monitoring
- Patients enroll in a patient registry

Implementation System

The Implementation System is the mechanism by which the pharmaceutical company monitors, evaluates, and improves elements to assure safe use. The systems are developed to confirm how REMS is implemented and if it can be improved at the practitioner level. Implementation systems provide the sponsor or manufacturer with the ability to monitor HCPs and facilities responsible for implementing REMS. To accomplish the analysis, the manufacturer needs access to data and to be able to rapidly change elements of the REMS if they are not be meeting expectations.

Timetable for Assessment (505-1(d))

Minimum FDA requirement 18 months, 3 years and 7 years after REMS approval (only compulsory element for all REMS programs)

APPENDIX B

FDA Evolution of Risk Management Regulations And Pharmaceutical Risk Programs²⁷

Year	Regulation	Result
1938	Federal Food, Drug, and Cosmetic Act (FDCA)	Designation of prescription drugs
1962	Full disclosure policy	Manufacturers provide product labeling to HCP with the following information: <ul style="list-style-type: none"> • Product's indication • Dosing • Side Effects
1970	Controlled Substances Act (CSA)	Regulates manufacturers, prescribers, dispensers, product labeling, warnings, and drug scheduling to provide additional indicators of risk and tools to manage those risks: <ul style="list-style-type: none"> • Boxed warnings • "Dear Healthcare Provider" letters
1976	21 C.F.R. § 310.501	First regulation to communicate risk to patients. Required for oral contraceptives and estrogen replacement products. <ul style="list-style-type: none"> • PPIs (Reviewed by FDA's Office of Drug Safety (ODS) staff and the Division of Drug Marketing, Advertising, and Communications)
1988		Restricted access to specific products with risks: Accutane Pregnancy Prevention Program (PPP) (Roche)
1990		Clozaril's "no blood, no drug" program (Sandoz) Registered physicians were required to submit weekly complete blood cell counts (CBCs) before receiving authorization to prescribe the product. The program required physicians, pharmacists, and patients to be enrolled in a registry to monitor compliance.
1998		The System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.™) required all patients, pharmacists, and physicians be registered and for female patients to be tested for pregnancy.
1999		Targeted Pregnancy Prevention Program (Roche)
1999	21 CFR 208	Medication Guides
2001		Accutane S.M.A.R.T. program (Roche) System to Manage Accutane-Related Teratogenicity
2005	FDA Guidance on Risk Mgmt	RiskMAPs (risk minimization action plans) to address safety monitoring and interventions: <ul style="list-style-type: none"> • Premarketing Risk Assessment • Development and Use of Risk Minimization Action Plans • Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment

		Plans require ongoing assessment and monitoring effectiveness of tools and interventions.
2006		<p>RiskMAP programs for:</p> <ul style="list-style-type: none"> • Tikosyn® (dofetilide) – T.I.P.S. • Tracleer® (bosentan) – T.A.P. • Plenaxis® (abarelix) – PLUS • Xyrem® (cataplexy-narcolepsy) • Mifeprex® (pregnancy termination) • Thalidomide <p>RiskMAPs with restricted distribution through performance-linked access systems:</p> <ul style="list-style-type: none"> • Clozaril® CARE System (Novartis) www.clozarilcare.com Teva Clozapine Patient Registry (Teva) Clozapine Prescription Access System (CPAS) (Mylan) FazaClo Patient Registry (AzurPharma Ltd.) <p>Novartis National Registries:</p> <ul style="list-style-type: none"> – United States: Clozaril National Registry (CNR) – National Non-Rechallenge Masterfile – United Kingdom and Ireland: Clozaril Patients Monitoring Service (CPMS) – Australia: Clozaril Patient Monitoring Service (CPMS) <ul style="list-style-type: none"> • Accutane iPLEDGE (Roche, Teva, Ranbaxy, Mylan) <p>RiskMAPs with restricted drug distribution:</p> <ul style="list-style-type: none"> • Lotronex® • Tysabri® TOUCH™ program
2007	Food and Drug Administration Amendments Act (FDAAA)	<p>FDA replaces RiskMAP requirements with REMS. FDA is given authority to:</p> <ul style="list-style-type: none"> • Require post-approval studies or clinical trials to assess a known or serious risk, or to learn more about a hypothetical serious risk • Require that new safety information be added to the product labeling • Require that companies submit Risk Evaluation and Mitigation Strategies (REMS) when deemed necessary to ensure that the product's benefits outweigh the risks <p>For marketed drugs, the manufacturer has 120 days to submit a proposed REMS.</p> <p>For new drugs, the manufacturer must include the proposed REMS as part of its New Drug Application (NDA) submission.</p>

APPENDIX C
New 2010 REMS Programs

(as of May 31, 2010)

1.	1/08/2010	Actema
2.	1/22/2010	Ampyra
3.	1/25/2010	Morphine Sulfate Oral Solution
4.	1/25/2010	Victoza
5.	1/25/2010	Videx
6.	2/02/2010	Oleptro
7.	2/02/2010	Xiaflex
8.	2/16/2010	Aranesp
9.	2/16/2010	Epogen/Procrit Injection
10.	2/26/2010	Janumet
11.	2/26/2010	Januvia
12.	2/26/2010	Wellbutin
13.	2/26/2010	Wellbutrin, Wellbutrin SR
14.	2/26/2010	Wellbutin XL
15.	2/26/2010	Zyban
16.	3/15/2010	Tasigna
17.	3/17/2010	Silenor
18.	3/22/2010	Vivitrol
19.	4/01/2010	Propylthiouracil
20.	4/5/2010	Oxycontin
21.	4/12/2010	Pancreaze
22.	4/20/2010	Zortress

APPENDIX D
Modified 2010 REMS Programs

(as of May 31, 2010)

1.	1/4/2010	Lyrica
2.	1/13/2010	Viramune
3.	1/29/2010	Kaletra
4.	2/2/2010	Savella
5.	2/19/2010	Tracleer
6.	3/5/2010	Promacta
7.	3/9/2010	Botox
8.	3/23/2010	Nplate
9.	3/24/2010	Exalgo
10.	3/24/2010	Exalgo Extended-Release Tablets
11.	3/25/2010	Pennsaid
12.	4/14/2010	Lamictal Extended Release
13.	4/16/2010	Effient (prasugrel)
14.	4/19/2010	Zonegran
15.	4/20/2010	Vimpat
16.	4/22/2010	Chantix
17.	4/29/2010	Colcrys (colchicines) Tablets

End Notes

¹ *The Checklist Manifesto: How to Get Things Right.*

² Robin Robinson, "REMS Take Hold," *PharmaVoice*, 9/2009, p.12,

<http://www.paragonrx.com/downloads/publications/PharmaVoice%20-%20REMS%20Take%20Hold%20-%20September%202009.pdf> (Accessed 5/17/2010)

³ US Food and Drug Administration. Risk evaluation and mitigation strategies for certain opioid drugs. *Federal Register*. 2009;74:17967-17970. Available at: <http://edocket.access.gpo.gov/2009/pdf/E9-8992.pdf> Accessed May 20, 2010.

⁴ Food and Drug Administration. December 4, 2009 FDA/Industry Working Group (IWG) Public Meeting on Risk Evaluation and Mitigation Strategies (REMS) for Certain Opioids. 2009. <http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm193499.htm>.

⁵ <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm200471.htm>

⁶ <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm>

⁷ <http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM164969.pdf>

⁸ BL 103951 ARANESP® (DARBEPOETIN ALFA) PROPOSED RISK EVALUATION AND MITIGATION STRATEGY (REMS) <http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM200104.pdf> Accessed 5/23/2010.

⁹ BL 103234 Epogen®/PROCRT® (Epoetin alfa) DRAFT REMS Document, 3 February 2010

<http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM200105.pdf>

¹⁰ NDA 22-272 OxyContin® Risk Evaluation and Mitigation Strategy.

http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022272s000remsOxycontin.pdf

¹¹ NDA 21-217 EXALGO™ (HYDROMORPHONE HYDROCHLORIDE) EXTENDED RELEASE TABLETS CII RISK EVALUATION AND MITIGATION STRATEGY (REMS)

http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021217s001REMSExalgo.pdf

¹² NDA 21-775 Entereg (alvimopan) RISK EVALUATION AND MITIGATION STRATEGY (REMS)

<http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm129511.pdf> Accessed 5/23/2010.

¹³ NDA 22-081 LETAIRIS Risk Evaluation and Mitigation Strategy

<http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM164969.pdf>

¹⁴ BLA 125268 Nplate (romiplostim) RISK EVALUATION AND MITIGATION STRATEGY (REMS)

<http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm129516.pdf> Accessed 5/23/2010.

¹⁵ NDA 22-266 ONSOLIS™ (fentanyl buccal soluble film) RISK EVALUATION AND MITIGATION STRATEGY (REMS) FOCUS™ Program for ONSOLIS™

<http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM187537.pdf> Accessed 5/23/2010.

¹⁶ NDA 22-291 PROMACTA® (eltrombopag) PROPOSED RISK EVALUATION AND MITIGATION STRATEGY (REMS)

http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022291s003REMSPromacta.pdf Accessed 5/23/2010.

¹⁷ Sabril Risk Evaluation and Mitigation Strategy

<http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM187533.pdf>

¹⁸ PROPOSED REMS FOR SUCRAID ORAL SOLUTION NDA 20-772 Sucraid (sacrosidase) Oral Solution

<http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM144251.pdf>

¹⁹ NEW SUPPLEMENT FOR NDA 21-290

Tracleer (bosentan) Risk Evaluation Mitigation Strategy - REMS MODIFICATION

http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021290s018REMS.pdf

²⁰ NDA 22-173 Zyprexa® Relprevv™ (olanzapine) Risk Evaluation Mitigation Strategy -

<http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM202330.pdf>

²¹ iPLEDGE Year 1 Review. <http://www.fda.gov/ohrms/dockets/ac/07/slides/2007-4311s1-04-sponsor-group.pdf>
Accessed 5/25/2010.

²² Abroms L, Maibach E, Lyon-Daniel K, Feldman SR. What is the best approach to reducing birth defects associated with isotretinoin? PLoS Med. 2006;3:e483.

²³ U.S. Food and Drug Administration Briefing document for iPLEDGE year one update.

²⁴ "Use of Medication Guides to Distribute Drug Risk Information to Patients," Gerald K. McEvoy, Pharm. D., FDA Public Hearing, June 12 and 13, 2007 <http://www.fda.gov/downloads/Drugs/DrugSafety/UCM173475.pdf>
Accessed 5/23/2010.

²⁵ "Nourjah P, Lee L, Kortepeter C, Avigan M, FDA Office of Drug Safety. National Survey of Pharmacists to Assess Awareness of Drug Risk Communication Tools; 2005.

²⁶ <http://www.fdpi.org/conf/handouts/Reshef.pdf>

²⁷ Deborah B. Leiderman, MD, Consulting Neurologist, CNS Drug Consulting LLC, Risk Management of Pharmaceutical Products at FDA— A Historical Perspective, 2008
<http://www.fdpi.org/conf/handouts/Leiderman.pdf>