Risk Evaluation and Mitigation Strategies (REMS): Past, Present, and Future

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Goals & Objectives

• Explain REMS and its attendant elements as it currently exists
• Assess the Impact of REMS in the Hematology/Oncology Marketplace
• Identify the Current Trajectory of where REMS is now and where it appears to be heading

REMS: stands for Risk Evaluation and Mitigation Strategy

REMS is the responsibility of the Food and Drug Administration (FDA) which is a branch of Health and Human Services (HHS)
Drug Safety Interested Parties

The management of drug safety and development of a systemic approach is of importance to:

• Drug Manufacturers
• Drug Regulators
• Drug Prescribers
• Drug Dispensers
• Drug Consumers

FDA History

• 1848 FDA created to conduct analysis of agricultural produce (currently the oldest consumer protection agency)
• 1906 Pure Food and Drugs Act (where’s the beef?)
• 1938 Federal Food Drug & Cosmetic Act – empowered the FDA with food & drug regulatory responsibilities
• 2002 Prescription Drug User Fee Act – allowed for the creation of RiskMAPS
• 2004 Year of Living Dangerously for FDA – Vioxx, Avandia and SSRI suicidal ideation

Where’s the Beef?

• [http://www.youtube.com/watch?v=Uq75diEyi40](http://www.youtube.com/watch?v=Uq75diEyi40)

• NOTE to editor or special forces – can we embed this video (beyond my technical prowess – of not please delete slide)
Recent REMS History

- REMS were created by the Food and Drug Administration Amendments Act (FDAAA) of 2007
- The statute gives FDA the authority to require a REMS from manufacturers to ensure that benefits outweigh risks for a drug or biological
- This legislation was touted as allowing drugs on to the market that otherwise would not be approved for use
- Plan was/is to have the manufacturer be responsible and own the process with collaborative FDA oversight as to the amount and final approval of content

FDA Website accessed 2/11/11

FDA and the Fluid Future

- The FDA may require manufacturers to develop REMS for both existing drugs and drugs in development
- This will be required when it determines special action is needed to ensure benefits of a drug outweigh its risk.
- REMS can facilitate FDA approval of drugs with a high-risk potential that would not otherwise be approved or allow a potentially dangerous drug to stay on the market.
- REMS present significant challenges for stakeholders, including patients, providers, cancer centers, payers, manufacturers, health information technology vendors, and regulatory agencies.

FDA Website accessed 8/21/10

REMS Stated Goals

- Institute of Medicine recommended back in 2006 that FDA have the explicit authority to require drug manufacturers to implement post marketing risk assessment and risk minimization programming
  1
- Actually “increase” the FDA drug approval rate
- Ensure drug safety in the approval process
- Decrease the risk of adverse events by examining those reported pre and post marketing and then determine if an intervention is required.

1 The Institute of Medicine Report issued September 22, 2006. The Future of Drug Safety: Promoting and Protecting the Health of the Public

FDA Website accessed 8/21/10
REMS Structure

- REMS are designed by the manufacturer to track and protect patients from a specific risk or risks of therapy.
- Based on draft guidance from FDA, REMS may facilitate access to medications by allowing medications with safety concerns to still be FDA-approved that otherwise would simply be rejected.
- Some REMS are simple (requiring only the use of a medication guide), while other REMS have numerous components and require actions by prescribers, pharmacists, pharmacies, and patients.

Two steps forward …

- FDAAA effective date was 3/25/2008
- RiskMAPs that were created prior to this date were left intact unless determined to have elements to assure safe use (ETASU)
- If ETASU were present then the RiskMAP was to be replaced with a REMS.
- Only Letairis (ambrisentan) and Tracleer (bosentan) required a REMS redo so the others are all still intact as plain RiskMAPs.

Pre REMS = Deemed Status

Drug and biological products deemed to have in effect an approved REMS are those that on March 25, 2008 (FDAAA effective date) had in effect 'elements to assure safe use' which include one or more of the following:

1. Health care providers who prescribe the drug have particular training or experience, or are specially certified
2. Pharmacies, practitioners, or health care settings that dispense the drug are specially certified
3. The drug is dispensed to patients only in certain health care settings, such as hospitals
4. The drug is dispensed to patients with evidence or other documentation of safe use conditions, such as laboratory test results
5. Each patient using the drug is subject to certain monitoring
6. Each patient using the drug is enrolled in a registry
MODIFIED LIST OF PRODUCTS DEEMED TO HAVE IN EFFECT AN APPROVED REMS

<table>
<thead>
<tr>
<th>Generic or Proper Name</th>
<th>Brand Name</th>
<th>Application Number</th>
<th>Date of Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eculizumab</td>
<td>Soliris</td>
<td>BLA 125166</td>
<td>3/16/2007</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>Revlimid</td>
<td>NDA 21–890</td>
<td>12/27/05</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>Tysabri</td>
<td>BLA 125104</td>
<td>11/23/2004</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>Thalomid</td>
<td>NDA 20–785</td>
<td>7/16/1998</td>
</tr>
</tbody>
</table>

1. New drug application (NDA); abbreviated new drug application (ANDA); biologics license application (BLA).
2. The original date of approval of the drug. FDA may have required elements to assure safe use at a later date.
3. Product is not currently marketed in the United States.
4. REMS element added afterward.

NOTE: FDA deemed 16 agents of which I have listed only 7 on this slide.

The Elements of REMS...

- Medication Guide
- Communication Plan
- ETASU
- Implementation System

Program Elements

- Medication Guide – Information specific to particular treatment explaining risk(s) to patient
- Communication Plan – Apparatus the manufacturer will utilize to notify the providers about REMS changes
- ETASU – Specific steps to be used to keep patients safe such as provider education or patient registries
- Implementation System – basically monitoring and evaluation of the above with improvement as the goal
- Assessment of REMS – Time table to assess REMS typically set at 1½, 3 and 7 years from FDA Approval
Medication Guide

1. The drug product is one for which patient labeling could help prevent serious adverse effects.
2. The drug product is one that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decision to use, or to continue to use, the product.
3. The drug product is important to health and patient adherence to directions for use is crucial to the drug's effectiveness.

Communication Plan

1. FDA may determine that a communication plan targeted at health care providers is a necessary element
2. May include sending letters to health care providers; disseminating information about REMS elements to encourage implementation or to explain safety protocols like monitoring by periodic laboratory tests
3. Possibly disseminating information to health care providers through professional societies about serious risks of the drug and any protocol to assure safe use

Elements To Assure Safe Use

1. For drugs shown to be effective but associated with a serious adverse drug experience and can only be approved if these elements were present
2. Or in a situation where a drug initially is approved without ETASU, but with other possible elements of a REMS that turn out not to be sufficient to mitigate such serious risk.
REMS Breakdown - February 2011

- Medication Guide = 177
- Communication Plan = 43
- Elements To Assure Safe Use = 21
- Implementation Plan = 16

Note that while all REMS have a medication guide, some will also have the three other elements added thus increasing the scrutiny and the bureaucracy burden.

FDA website last accessed 2/19/2011

REMS since creation

- As of 2/19/2011 there exist 177 REMS on the books at FDA (excluding drugs with “deemed status”)
- There were only 136 REMS on the books when this was presented at the ACCC-OPEN meeting in St. Louis 6 months ago...
- Only 11 are drugs used in the hematology/oncology world
  - All except interferon are oral/therapy
  - All were created/modified within the last 18 months
  - None are “traditional” chemotherapy
  - 31 could be viewed as supporting heme/onc
  - 18 have a place in infusion centers (25 if antibiotics are included)
  - Ultimately an argument could be made that ambulatory clinics could see as many as 82 different REMS!

REMS – OPEN 9/29/2010

- 136* REMS on the books
- 6 are used in Heme/Onc
- Interferon only non-oral
- None are traditional drugs
- 31 support Heme/Onc
- 11 outpatient clinic use
- (18 if you add antibiotics)
- 55 Total REMS (~40%)

ACCC National 3/26/2011

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- 11 are used in Heme/Onc
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* Excluding Deemed Status and valid as of 2/19/11

Time Changes Things

ACCC – OPEN 9/29/2010

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Trending up …

- According to ASHP about 1/3 of new molecular entities and biologic products approved by the FDA in the first half of 2010 had a REMS required
- 113 REMS where FDA approved as of mid-February 2011 (177 if versions are counted)
- The general consensus / concern is that as we move forward there will be even more …

Oncology Specific REMS

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Date of REMS</th>
<th>REMS Components</th>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Everolimus (Sotrensis)</td>
<td>4/2010</td>
<td>Medication Guide; Communication Plan</td>
<td>NDA - Oral</td>
</tr>
<tr>
<td>Interferon Alfa 2b (Intron-A)</td>
<td>5/2008, 8/7/08 mod</td>
<td>Medication Guide</td>
<td>B/LA - Inj</td>
</tr>
<tr>
<td>Lenalidomide (Revlimid*)</td>
<td>8/3/10</td>
<td>Medication Guide; ETASU Implementation System</td>
<td>NDA - Oral</td>
</tr>
<tr>
<td>Sunitinib (Sustiva*)</td>
<td>7/1/10</td>
<td>Medication Guide</td>
<td>NDA - Oral</td>
</tr>
<tr>
<td>Nilotinib (Tasigna*)</td>
<td>3/15/10, 6/17/10 mod</td>
<td>Medication Guide; Communication Plan</td>
<td>NDA - Oral</td>
</tr>
<tr>
<td>Thalidomide (Thalomid*)</td>
<td>8/2010</td>
<td>Medication Guide; ETASU Implementation System</td>
<td>NDA - Oral</td>
</tr>
<tr>
<td>Pazopanib (Votrient*)</td>
<td>10/18/09, 4/27/10 mod</td>
<td>Medication Guide</td>
<td>NDA - Oral</td>
</tr>
</tbody>
</table>

Drugs requiring ETASU

- Algucosidase Alfa
- Aloxatron
- Alemtuzumab
- Ambisentan
- Bosentan
- Buprenorphine
- Buprenorphine w/ Naloxone
- Darbepoetin Alfa
- Eculizumab
- Eltrombopag
- Epoetin Alfa
- Fentanyl
- Hydromorphone
- Isotretinoin
- Lenalidomide
- Olanzapine
- Oxycodone
- Romiplostim
- Sacrisidase
- Thalidomide
- Vigabatrin

Color = Likely Heme/Onc Amcare Use (12 of 21)
Inherent Flaw?

- REMS can ensure safe use of prescribed drugs, including appropriate patient selection, monitoring and education.
- However, as the number and complexity of the REMS initiative increases, the challenges associated with prescribing and dispensing the drug increases as well.
- The consensus of the recently empanelled NCCN working group was that REMS may add significant workload to prescribers and dispensers of drugs with REMS, making it potentially less likely for a drug with a complex REMS to be used at all.

A Difficult Challenge

- Therefore REMS must be designed so that they:
  - Do not impose an inappropriate burden on patients
  - Do not impose an inappropriate burden on physicians
  - Do not impose an inappropriate burden on pharmacists
  - Do not impose an inappropriate burden on healthcare providers, including hospitals and physician practices
- The application of REMS must balance feasibility for providers and pharmacists with the FDA’s goal of mitigating the risks of a drug; in the end it must be serviceable and make sense.

For Example … Darbepoetin

There are ‘only’ two stated goals for the REMS program for Darbepoetin (Aranesp):

1. To support informed decisions between patients and their HCPs who are considering treatment with Aranesp by educating them on the risks of Aranesp.
2. For treatment of patients with cancer, the goal of the REMS, as implemented through the ESA APPRISE (Assisting Providers and cancer Patients with Risk Information for the Safe use of ESAs Oncology Program), is to mitigate the risk of decreased survival and/or poorer tumor outcomes.
Darbepoetin ESA APPRISE

- **Medication Guide:** Retail dispensing or use in physician office/clinic/hospital outpatient
- **Communication Plan:** How to explain what’s new
- **ETASU:** Ensure that appropriately licensed healthcare providers who prescribe and facilities that administer or dispense Aranesp for patients with cancer in private practice and hospitals or outpatient clinics are certified.

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Aranesp REMS by the numbers

- 13
- 4863
- 464
- 27,103
- 32,000
- 190


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Imagine 177+ versions …

Drug Z₁₀-th
Imagine if you will …

Opposing Forces inherent in REMS

REMS from the Users Viewpoint

- Pharmacist (Inpatient/Outpatient/Retail)
- Nurse (Exam/Treatment/Triage)
- Physician (Individual/Practice)
- Hospital (Inpatient/Outpatient)
- Manufacturer (Users/Payers)
- Regulator
- Patient
REMS Perspective: Community Hospital (Inpatient/Acute)

- Typically multidisciplinary in nature (doctors, pharmacists, nurses, social workers, case managers, billers & coders)
  - Historically had systemic slack to handle extra reporting requirements
- Inpatient pharmacy departments are typically a cost center
  - Typically ANY incremental cost is bad and to be avoided or fought
- Both Non & For-Profit concerned about expenses & revenues
  - Regardless of environment, there is pressure to contain costs
- Staffing budgets are tight or shrinking and management is overwhelmed
- Can we dismantle or greatly curtail existing & future REMS?
  - On-line clearing house or instant adjudication?
  - EMR or CPOE will be of assistance in the future?
- Can we reduce burden to near zero or generate revenues?

REMS Perspective: Community Hospital (Outpatient/Amcare)

- Also typically multidisciplinary in nature (doctors, nurses, pharmacists, social workers, case managers, billers & coders)
  - Pharmacists, financial counselors, social workers and case managers are increasingly tasked with patient assistance programs
- Outpatient = revenue center
  - Remuneration CMS ~ ASP+5% presently (margins trending very thin)
- Both Non & For-Profit concerned about expenses & revenues
  - Regardless of environment there is pressure to contain costs
- Regardless of environment there is pressure to generate revenue
- Can we dismantle or greatly curtail existing & future REMS?
  - On-line clearing house or instant adjudication?
  - EMR or CPOE will be of assistance in the future?
- Can we reduce burden to near zero or generate revenues?

REMS Perspective: Community Clinic (Physician’s Office)

- Not radically different from Hospital but paid as either free-standing clinic (FSC) or physicians office (majority of oncology care)
  - Physician Office CMS ~ ASP+5% (fee schedule)
- Typically multidisciplinary in nature but greatly reduced as all staff costs come at expense of profit
  - Pharmacists rare or stretched very thin (at present)
- Keenly aware of expenses
  - Will analyze to determine what therapies really cost (including non-funded mandate!)
- Many sites actively attempting EMR but oncology specificity is hard
  - If not begun immediately, no ARRA incentive will be available to offset costs
- Even sites with an EMR have manual reporting for REMS
  - Of what benefit is an EMR if a manual scan is required and takes storage space?
- Model predicts that financial incentives drive business
  - Cost neutral to profitable required or little to no use of REMS products
REMS Perspective: Manufacturers Issues

• REMS represent a chance to ensure appropriate use but at the cost of possibly becoming too onerous for prescribers to even consider
• The oncology cost escalator is reputed to be much higher than the cost of other medical specialties
  – Costs are high everywhere but the current rate of increase is unacceptable
  – CMS deep throat “We are deeply concerned about ensuring there are no future $2 billion dollar drugs here at Medicare”
• “Likely” Outcomes for REMS and the payer take on it
  – Reduced use of any FDA approved drugs with a REMS attached - may be attractive to payers, provided the next therapy in line is not more expensive
  – Potential short-circuiting of any safety device due to clinical disregard and staffing pressures to just click or sign anything to get the drug - very concerning to everyone but most definitely to payers as then safeguards are not active and costs could rise
  – By selecting out bad performance patients this may reduce the use of therapies to more appropriate candidates – a payer plus
  – Self-fulfilling prophecy of reduced adverse events due to reduced reporting or reduced use but not from the intended programming safeguards

“REMS is an opportunity to improve patient care and support all stakeholders”

• Improve effectiveness
  – or generate more bureaucracy and actually distracting clinicians?
• Improve efficiency
  – or pretend that filing paperwork is the same as clinical practice?
• Add safety and thereby value
  – or detract from novel drug use and increase administrative costs?

Current State of Affairs

• REMS could be helpful to clinicians and patients alike except
  – The current view by the medical establishment is one of distrust and disgust or at a minimum what could be called “healthy cynicism”
  – There are historical cases of financial abuses of drugs (ESAs - used primarily as a profit source) and safety concerns (Opioids - use can always be improved)
  – Requiring extra steps per drug encounter that REMS programs have traditionally and presently require … is going to greatly limit that drug use in some settings
• To be effective, any REMS program cannot add to the increased administrative burden to any significant degree
  – Many physicians are claiming they spend hours each week on bureaucratic entanglements (mainly for reimbursement) rather than patient care
  – Any staff time that is increased either adds to the cost of care or reduces other care
  – Or potentially risks circumventing those exact safety measure due to pressures inherent in the system
2009 HOPA Pharmacist Survey

- 75% Educate both providers & patients
- 70% Enroll patients
- 40% Transfer between sites
- 25% Pharmacist should NOT be involved

Study conducted of Hematology Oncology Pharmacy Association (HOPA) active pharmacist membership in March 2009 with 152 responses

Are Oncology REMS Necessary?

- REMS arose not from the serious risks of medications but rather the concern that black box warnings and labeling recommendations were being overlooked
- Oncology is slightly different in that:
  - We are multidisciplinary more than other specialties
  - We use drugs known to be toxic that require extra monitoring
  - Terminal patients are motivated to be treated aggressively
  - We provide extra counseling and supportive care for patients
  - The costs inherent in Oncology already warrant extra scrutiny

NCCN Work Group REMS Recommendations

- Standardization of REMS Processes to Allow for the Provision of Efficient Care
- Assessment of REMS Programs
- Improvement of REMS Programs associated Medications Guide and Overall Health Literacy
- Incorporation of REMS into Institution Clinical Practice
- REMS and Off-Label Drug Use
- Provider Knowledge and Acceptance of REMS
- Minimization of Provider Burden
- Compensation for Complying with REMS Requirements
NCCN REMS Status …

- The presentation to the FDA 5/2010 did generate verbal responses that agreed that suspension and review would be prudent.
- The NCCN Task Force on REMS finished its recommendations and they have been published in a JNCCN supplement 9/2010.
- Overall the Work Group has served as a useful conduit for feedback and focus.

REMS Public Hearing – July 2010

We have limited data to show how effective these REMS interventions are, and what is the cumulative effect of the burden and other effects of these programs on health care in general, as well as on health, on patient safety.

Janet Woodcock, MD - Director, FDA - CDER

U.S. Food and Drug Administration

http://www.fda.gov/Drugs/NewsEvents/ucm210201.htm

REMS … Future Directions

- The 800 pound gorilla … Could we do away with these or greatly curtail them? The answer is of course 'no' but it had to be asked.
- Bureaucracy never diminishes nor self limits once created – T. Tyler
- Congress passed a law – should we propose amending, repealing it?
- Admitting you have a problem is the first step ...
- If the REMS programs are unique and burdensome they will reduce the drugs uptake and eventually industry may not bring these drugs to market … at all!
- Industry wants safe, effective drug sales …
- Clinicians want safe and effective agents to use with minimal interference between them and their patients …
- Patients want what's best …
- Payers want what's efficacious at a reasonable cost …
- You just want me to end on time …
QUESTIONS?