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**EDUCATIONAL SESSION ABSTRACT**  
**2010 ASHP Midyear Clinical Meeting**  
**Anaheim, California**

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**232-2**

**Overview of Risk Evaluation and Mitigation Strategies : FDA REMS Processes and REMS Challenges**

Worthy, K.C.

Food and Drug Administration, 10903 New Hampshire Ave, Bldg 22, Rm 2428  
Silver Spring, MD 20993-0002, USA. Email: [Kendra.worthy@fda.hhs.gov](mailto:Kendra.worthy@fda.hhs.gov)

Certain drug and biological products submitted for approval or approved under sections 505(b) or 505(j) of the Federal Food, Drug, and Cosmetic Act (FDCA), or section 351 of the Public Health Service Act (PHS Act) are required by FDA to have a Risk Evaluation and Mitigation Strategy (REMS) to ensure the benefits outweigh the risks. An overview of the REMS review process, including understanding a product's risks, determining the need for a REMS, and the appropriate REMS components required will be provided, along with a description of the REMS assessment review process. Key lessons and challenges encountered with REMS components such as Medication Guides, communication plans, elements to assure safe use, and REMS assessments will also be examined.

**Learning Objectives:**

1. Describe the basic elements of Risk Evaluation and Mitigation Strategies.
2. Describe the key steps in the Risk Evaluation and Mitigation Strategy review process.
3. List at least three challenges encountered with REMS components and/or REMS assessments.

**Self-Assessment Questions:** (True or False)

1. A REMS can include a Medication Guide, a Boxed Warning, and Elements to Assure Safe Use.
2. The most serious preventable risks will lead to the most restrictive programs.
3. While a representative sample of healthcare providers participate in REMS assessment surveys, it is difficult to obtain a representative sample of patients.

**Answers:** 1. (F); 2. (T); 3. (F)

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**SUPPLEMENTAL HANDOUT**  
**2010 Midyear Clinical Meeting**  
**Anaheim, California**

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**\*\*Materials not provided by presenter in time to meet publication deadline\*\***

**Living with REMS: Case Studies and Best Practices**

**ACPE Activity #204-000-10-233-L04P**

**2.0 Contact Hours / Knowledge-based**

***Moderator:** JoAnn Stubbings, BSP Pharm, MCHA, Manager, Research and Public Policy and Clinical Associate Professor, University of Illinois at Chicago*

**Presentation:**

**Overview of Risk Evaluation and Mitigation Strategies**

*Kendra Worthy*

**Speaker Contact Information:**

Kendra Worthy

FDA

10903 New Hampshire Ave

Bldg 22 Rm 2428

Silver Spring, MD 20993

Email: [Kendra.worthy@fda.hhs.gov](mailto:Kendra.worthy@fda.hhs.gov)

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**233-2**

**ASHP Response and Advocacy**

Chen, D.

American Society of Health-System Pharmacists, 7272 Wisconsin Ave, Ste 200,  
Bethesda, MD 20814, USA. Email: [dchen@ashp.org](mailto:dchen@ashp.org)

The American Society of Health-System Pharmacists works with its members and stakeholder organizations to address the challenges of Risk Evaluation and Mitigation Strategies. Key issues ASHP has been addressing are (1) Patient safety needs improvement, (2) REMS are burdensome to practitioners and patients, (3) REMS are law and are a part of the medication use system, (4) Practitioners need resources and best practices to integrate REMS into the continuum of care, (5) We need to ensure REMS are effective, and (6) We need to evaluate the overall impact on the medication use system.


**Learning Objective:**

Participants will be able to describe advocacy activities and practitioner resources on the issues of REMS being supported by ASHP

**Self-Assessment Question:**

Improvements in the application and implementation of REMS will require:

- a. Advocacy for improved standardization of REMS
- b. Continuing education for practitioners on the details of REMS
- c. Avoidance of using REMS medications
- d. Assessment of efficacy of REMS and impact on medication use system
- e. all of the above
- f. a,b,d



## ASHP Response and Advocacy

David Chen, R.Ph., MBA  
Director, Pharmacy Practice Sections  
American Society of Health-System Pharmacists

### Defining the Issues

- Patient medication safety needs improvement
- REMS are burdensome to practitioners and patients
- REMS are law and are a part of the medication use system
- Practitioners need resources and best practices to integrate REMS into the continuum of care
- We need to ensure REMS are effective
- We need to evaluate the overall impact on the medication use system

### Balancing Medication Safety and Access for All Patients




### ASHP Advocacy

- Testimony and comment letters
- Push for standardization
- Requests for clarifications
- Feedback on need to assess outcomes and burden
- Active stakeholder participant in multiple settings
- Patient advocate on need to assess unintended consequences

### ASHP Education & Organization Focus

- Task Force on Serving Patient Care for by Specialty Suppliers
- Education sessions at Summer 2009, MCM 2009, Summer 2010, and MCM 2010
- AJHP papers and editorials published
- AJHP interest in seeking papers on topic area
- Various web based C.E. programs



### ASHP Resources

Navigation: Home | Practice and Policy | Resource Centers | RSS

**PRACTICE AND POLICY**

- Resource Centers
  - Anticoagulation Resource Center
  - Compounding Resource Center
  - Contrast Media and Medication Management
  - Drug Shortages
  - Evidence-Based Practice
  - H1N1 Flu Resource Center
  - Influenza
  - Investigational Drug Services
  - Patient Safety
  - Patient Assistance Programs
  - Public Relations Network Resource Center
  - Quality Improvement Initiative (QI)
  - Risk Evaluation and Mitigation Strategies Resource Center
  - Small and Rural Hospital
  - Tobacco Cessation

**Risk Evaluation and Mitigation Strategies Resource Center**

The Risk Evaluation and Mitigation Strategies (REMS) were created by the FDA to serve as a post-marketing surveillance process that ensures medication safety. This resource center contains basic information for pharmacists, patients and other healthcare professionals about REMS, as well as other medications that are managed through other medication risk management programs or RDDS outside of the REMS processes.

**Access the REMS Database**

ASHP's easy to use database containing basic information about each medication along with a risk management program. Links to useful websites are located throughout. Use the alpha list on the right to select from the generic drug name.

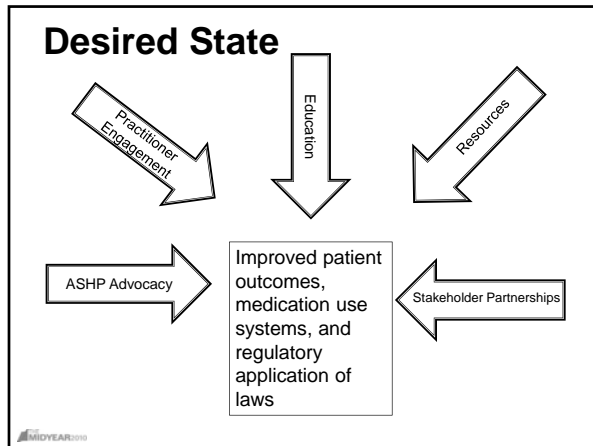
- ☐ A to G...drug listed by generic name
- ☐ I to P...drug listed by generic name
- ☐ Q to Z...drug listed by generic name

**What are REMS & RDDS?**

REMS are post-marketing surveillance processes created by the FDA to ensure drug safety. Previous risk management programs were classified as Risk Minimization Action Plans and Restricted Drug Distribution Systems (RDDS). [Read more](#)

**Even More Information**

Updates on all medications can be found in the [CDER Drug Database](#) or on the [manufacturer's website](#).



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**233-3**

**REMS and the P&T Committee**

Fotis, M.A.

Northwestern Memorial Hospital, 251 E Huron, Feinberg LC700, Chicago, IL 60611, USA. Email: [mfotis@nmh.org](mailto:mfotis@nmh.org)

It is time to improve the safety of newly approved medications. Health organizations need to enhance their capability to react to safety concerns raised by recent studies. Pharmacists need to help patients play a more active role in medical decisions. The committee can collect observational data about the safety of medications as warnings and advisories are published. The P&T Committee at Northwestern Memorial Hospital includes REMS strategies in the formulary request, formulary monograph, formulary recommendation, and in post approval analysis. Recent committee actions involving REMS associated medications are discussed. The results of a recent survey of REMS baseline understanding of the NMH Clinical staff are summarized. Action strategies to improve REMS understanding and enhance medication safety practices are summarized. We do not need another form or checklist. We need to act. It's about time.

**Learning Objectives:**

1. Describe at least two strategies to prepare the P&T committee for a world with REMS.
2. Explain how the committee can use REMS requirements to advance medication safety.
3. List at least four goals of a successful committee response to REMS/ ETASU programs.


**Self-Assessment Questions:** (True or False)

1. Stapling computer generated printouts to a bag is an effective strategy to involve patients in medical decision making.
2. Physicians, pharmacists, and nurses are already fully informed about REMS.
3. Developing forms to meet the letter of regulations is the same as improving safe outcomes.

**Answers:** 1. (F); 2. (F); 3. (F)

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**REMS and the P&T Committee**



Michael A. Fotis  
 Manager Drug Information  
 Residency PGY1 Director  
 Northwestern Memorial Hospital / Chicago

**Audience Background**

Please raise your hand if your response is yes to the following questions:

- P&T Member?
- P&T Leadership Role? (set agenda, frame issues)
- REMS based Drug Use Policy Concerns are resolved and the Process is Operating in a Flawless Manner?
- You would like REMS to go away?

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**Personally** I want to fully support these goals:

**I regard the goals of the REMS regulations:**

- Improve the safety of selected newly approved medications.
- Enhance the capability to react to safety concerns raised by recent studies.
- Help patients play a more active role in medical decisions.
- Collect observational data about the safety of selected medications.

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**Changes to Committee Practices**

REMS/ ETASU included in:

- Formulary Request
- Formulary Monograph
- Formulary Recommendation
- On-Line Formulary

- Pharmacists to sponsor Formulary Action for newly invoked REMS/ETASU/RDDS.

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**Formulary Request Form**

Example: Tolvaptan

There are 4 steps to add a medication to the Formulary:

1. Disclosure of potential conflicts of interest with Otsuka the manufacturer of tolvaptan (Samsca™).
2. Submit a protocol for the use of this medication in patients at NMH. Your protocol should summarize the evidence supporting your recommendation and also include the indications, patient selection, status (first line, alternative agent etc), and precautions that you recommend. A typical protocol is one or two paragraphs in length.

Risk Evaluation and Mitigation Strategy (REMS): A REMS is enacted because of increased risks associated with overly rapid correction of serum sodium leading to osmotic demyelination. Each patient is to receive an FDA approved Med Guide. Please describe your plan for compliance.

**Formulary Request**

Tolvaptan continued

Why are we doing this, what problem are we trying to fix? Why do we need this medication?

Is the proposed protocol consistent with the best available evidence?

Does the protocol address all of the predictable concerns about the safety of the new practice?

Will the proposal have an effect on cost?

Are there any measurable outcomes and is there a plan to assess and report these outcomes?

3. Identify inferior, and or superfluous medications that should be removed from the Formulary.
4. If the evidence supports superiority of these products you will be asked to present your protocol (10-15 minutes) at a Formulary Committee meeting.

Item	P&T Monograph	Finding / URL
Product dedicated website	<a href="http://www.samsca.com/">http://www.samsca.com/</a>	
FDA News Item	FDA Approves Samsca to Treat Hyponatremia (May 22, 2009) <a href="http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm1161945.htm">http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm1161945.htm</a>	
REMS	A Risk Evaluation and Mitigation Strategy (REMS) is intended to manage a known or potential serious risk associated with a drug or biological product. A REMS will be required of the sponsor if the FDA believes it necessary to ensure that in use, the benefits of the drug or biological product outweigh its risks. A REMS can include a Medication Guide, Patient Package Insert, a communication plan, elements to assure safe use, and an implementation system, and must include a timetable for assessment of the REMS. List of other drugs with REMS is at: <a href="http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm">http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm</a>	The company was required to implement a REMS by the FDA. <a href="http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM187491.pdf">http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM187491.pdf</a> The REMS is required in order to decrease to lessen the potential risk of osmotic demyelination syndrome (ODS) by: <ul style="list-style-type: none"> <li>Educating healthcare providers on the risk of overly rapid correction of serum sodium associated with tolvaptan and the need for initiating tolvaptan in a hospital to ensure proper titration and monitoring</li> <li>Informing patients of the serious risk associated with the use of tolvaptan, particularly the risk of osmotic demyelination syndrome</li> </ul> Elements of the REMS include: <ul style="list-style-type: none"> <li>Medications Guide</li> <li>Communication Plan to Healthcare Professionals - involved in the prescribing, purchasing, dispensing or administration for both inpatient and outpatient settings at time of launch. (See details in following row)</li> </ul>
	Bill Budris	

## Committee Recommendation:

Tolvaptan is restricted to hepatologists, and intensivists. Use is restricted to FDA approved indications.

Orders for fluid restriction must be discontinued when tolvaptan is initiated.

Medication Guide must be selected when Tolvaptan is ordered.

IDENTIFIED ORDER: Tolvaptan (Samsca)

Link to Medication Guide

Drug Reference | Education/Leaflet | Reference

Tolvaptan (Samsca)

Tolvaptan FDA REMS

For more prescribing information, see the following:

Krista Engelmann

## Recent Experiences

Medication	REMS	Formulary Sponsor	Action
Tolvaptan (Otsuka)	Medication Guide	Unaware of REMS	Added to restricted formulary
Alvimopan (Adolor)	E.A.S.E. Program (ETASU)	Unaware of REMS*	Rejected
Romiplostim (Amgen)	NEXUS (ETASU)	Aware but voluntary	Proposal withdrawn
Deferasirox (Novartis)	RDDS rather than REMS EPASS Care System	Unaware	Proposal for off-label use tabled
Epoetin Alpha (Amgen)	APPRISE (ETASU)	Aware but assumed inpatients were exempt	Possibly to Restrict use from oncology patients

\* Vendor induced Formulary Request

## Recent Experiences

Medication	REMS	Formulary Sponsor	Action
Pradaxa (dabigatran)	Medication Guide	Unaware of REMS*	Sponsor disqualified
			What did we decide?

\* Formulary Sponsor hoping to serve as a paid speaker

## REMS SURVEY


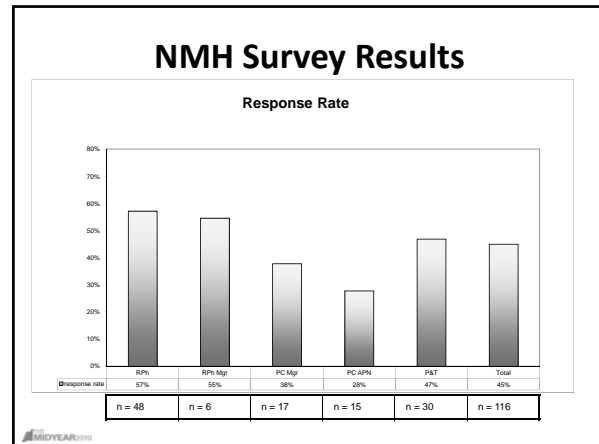
Survey Designed and Conducted by  
 Bill Budris Drug Information  
 Pharmacist  
 Northwestern Memorial Hospital

### REMS Survey

Web-based NMH survey, September 13-21, 2010

Survey Targets (n= 258)


- Staff pharmacists (84)
- Pharmacy Managers (11)
- Nursing Managers (45)
- Advanced Practice Nurses (54)
- P&T members other than RPhs (64)

### Survey Results (n = 116)


**73.3% identified REMS correctly but otherwise REMS and implications poorly understood**

- Asked if adequately informed about REMS  
6% said yes
- Asked if REMS known to improve patient safety  
65.2% unsure
- Asked to identify ETASU 36% were correct
- Asked if ETASU reduced serious medication errors  
66% unsure




### Survey Results

- Asked if role clear with respect to REMS drugs used in practice area:
  - Role not clear 89.7%
- Asked which professionals are responsible for compliance with REMS:
  - All are responsible 46.6%
  - Not Sure 41.4%




### Survey Results

- Asked if off-label use of ETASU drugs will be possible: 75.9% unsure
- Asked if concerned time will be taken from other patient care: 62.1% unsure
- Asked where they first learned of REMS: 54.9% this survey
- Asked who requires REMS: 44% correct - FDA
- Asked if had direct REMS contact: 16.8% had



### Survey Results

- Asked about challenges when patient receives Med Guide before a first dose:
  - How to handle non English-speaking, illiterate, unconscious, cognitive issues, or if raises questions  
Don't know 87.9%



**Actions**

What did we do about it?

- REMS/ ETASU 101 presented to Medical Staff Leadership
- REMS/ETASU 101 presented to P&T Committee Leaders and Members
- REMS/ETASU 101 presented to NMH Pharmacy Staff
- REMS/ETASU 101 presented at Nursing Grand Rounds

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<p><b>The Time has Come</b></p> <ul style="list-style-type: none"> <li>▪ Let's not limit our focus to forms, and procedural.</li> <li>▪ I recommend we venture away from our silo, and focus on outcomes:</li> </ul>	<p><b>It is Time to:</b></p> <ul style="list-style-type: none"> <li>• Improve the safety of newly approved medications.</li> <li>• Enhance the capability to react to safety concerns raised by recent studies.</li> <li>• Help patients play a more active role in medical decisions.</li> <li>• Collect observational data about the safety of medications.</li> </ul>
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**It is Time to:**

<p><b>GOALS</b></p> <ul style="list-style-type: none"> <li>• Improve the safety of newly approved medications.</li> <li>• Enhance the capability to react to safety concerns raised by recent studies.</li> <li>• Help patients play a more active role in medical decisions.</li> <li>• Collect observational data about the safety of medications.</li> </ul> <p><b>Thank You!</b></p>	<p><b>ACTIONS</b></p> <ul style="list-style-type: none"> <li>▪ Conduct post- Formulary approval use studies of clinical outcomes</li> <li>▪ Focus studies on safety concerns</li> <li>▪ Go beyond stapling a computer generated handout to a paper bag</li> <li>▪ Continue to focus Committee sponsored use studies on safety concerns</li> </ul> <p><b>Its about Time!</b></p>
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**2010 ASHP Midyear Clinical Meeting**  
**Anaheim, California**

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**233-4**

**Elements to Assure Safe Use (ETASU): Outpatient**

Chan, J.

University of Illinois at Chicago, 833 South Wood Street, Room 164, Mail Code 886, Chicago, IL 60612, USA. Email: [jchan@uic.edu](mailto:jchan@uic.edu).

The Food and Drug Administration requires manufactures to develop Risk Evaluation and Mitigation Strategies (REMS) to manage and ensure that the benefits of a medication outweigh its risks when serious potential adverse effects are known. The components of a REMS program may include one or a combination of the following: Medication Guide, Patient Package Insert, a Communication Plan, and/or Elements to Assure Safe Use (ETASU). The REMS with ETASUs has generated significant discussion as health care providers find REMS to be complex, time consuming and burdensome. The paper work associated with REMS may be onerous, especially those associated with ETASUs. The strain on the health care system increases as more drugs with REMS are developed; especially with the limited availability of resources to ensure that all the elements associated with the REMS are met. A medication with REMS and ETASU will be discussed; including compliance rates at a University Outpatient Care Center. Additionally, methods on improving REMS with ETASUs compliance rates in this setting will be presented.

**Learning Objectives:**

1. Review the impact of REMS requirements on the health system and the medical providers.
2. Review compliance rates of a medication with the REMS with ETASU requirement.
3. Discuss methods for improving REMS with ETASU compliance rates at a University Outpatient Care Center.

**Self-Assessment Questions:** (True or False)

1. REMS requirements are mandated by the FDA to minimize potential and serious adverse effects.
2. REMS with ETASUs requires minimal resources and time to monitor patients for any adverse effects.
3. Hiring a pharmacy technician or pharmacy student may be a viable choice to improve REMS compliance rates.

**Answers:** 1. (T); 2. (F); 3. (T)

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## Elements to Assure Safe Use (ETASU): Outpatient

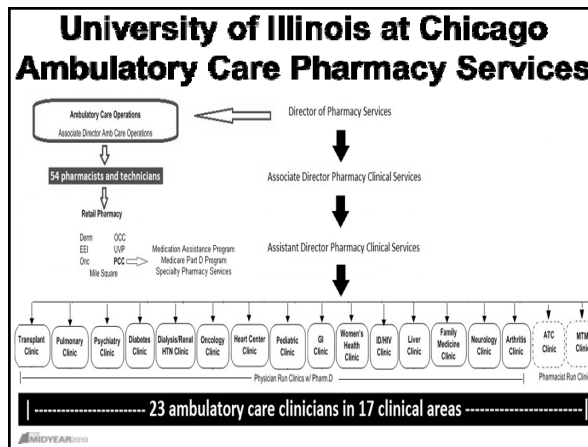
Juliana Chan, Pharm.D.  
Assistant Director Pharmacy Clinical Services  
Clinical Assistant Professor,  
Department of Pharmacy Practice College of Pharmacy and  
Department of Medicine, Sections of Digestive Diseases & Nutrition and  
Section of Hepatology, College of Medicine

## Outline of Presentation

- Present a case study with REMS associated with ETASU
- Review compliance rates with a REMS with ETASU medication
- Discuss methods on improving REMS with ETASU compliance rates at a University Outpatient Care Clinic

## University of Illinois Medical Center (UIMC)

- Comprehensive state teaching and research hospital
- 480-bed hospital with approximately 40 primary care and specialty outpatient clinics
  - Center of Excellence: Women's Health, Solid Organ Transplant, Robotic Surgery, Ophthalmology
- Estimated staff # of 2400

## Bosentan Patient Case

### 72 YOBF w/ PAH on bosentan since 2005

**PMH**  
Type 1 DM, HTN, HL, non-obstr CAD, severe PAH, hirsutism, microcytic anemia, asthma/COPD, seasonal allergies, diverticulosis and tubular adenoma, adrenal adenoma, vitD deficiency, hypercalcemia, hyperparathyroidism

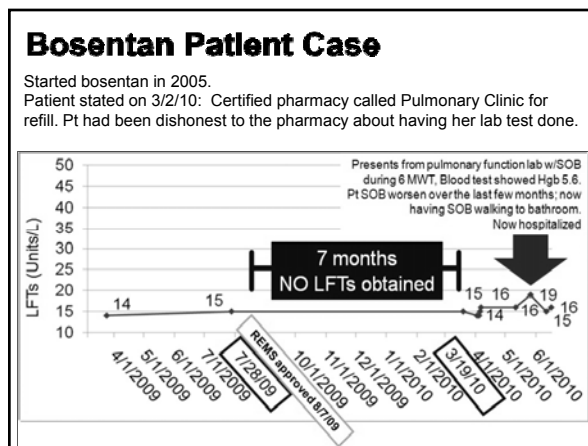
**Social History**  
Smoked 1-2 PPD x 25-30 years; quit 1985 occasional EtOH

**Medications**  
Albuterol neb as needed  
aspirin 325mg daily  
bosentan 125 mg twice daily  
cholecalciferol 50,000 intl units daily  
felodipine 10 mg daily  
fluticasone- salmeterol 500/50 mcg 1 puff bid  
furosemide 40 mg twice daily  
guaifenesin 100 mg four times daily  
hydrochlorothiazide 25 mg daily  
ibuprofen 400 mg every 6 hours  
insulin glargine 50 units at bedtime  
metformin 850 mg twice daily  
metoprolol 100 mg twice daily  
ranitidine 150 mg twice daily  
simvastatin 80 mg at bedtime  
tiotropium 18 mcg inhalation capsule daily

**Studies**

PFTs	Measured	% Predicted
FVC (L)	3.22	116.06
FEV1 (L)	1.52	70.55
FEV1/FVC (%)	47.11	
TLC (L)	6.06	107.68
DLCO (ml/min/mm Hg)	3.56	17.38

**6 minute walk test**  
At the end of 6 min of ambulation the VS were pulse 100 bpm, BP 136/77, SPO2 89% on 10 lpm of O2 thru nasal cannula. After 1 min of recovery the VS were pulse 80 bpm BP 144/72 mm Hg and SPO2 91% on room air.



### Bosentan REMS with ETASU

- Bosentan indication
  - Treatment of pulmonary arterial hypertension (PAH) (WHO Group I) in patients with WHO Class II-IV symptoms, to improve exercise ability and decrease the rate of clinical deterioration
- Bosentan can cause severe adverse effects
  - "bosentan (Tracleer®) caused at least 3-fold ULN\*\* elevation of ALT and AST in about 11% of patients..."
  - "In animal studies, bosentan caused teratogenic effects including malformations of the head, mouth, face, and large blood vessels."

REMS  
with  
ETASU

\*Elements to Assure Safe Use  
\*\*Upper limit of normal

http://www.accessdata.fda.gov/drugsatfda\_docs/label/2009/021290s012bl.pdf  
http://www.tracleer.com/Hcp-Start-Tracleer-First-Warnings

### Bosentan REMS with ETASU

- Enroll patients in bosentan (Tracleer®) Access Program
- Counsel patients on risks of bosentan
- Review baseline LFTs and if applicable, pregnancy test
- bosentan (Tracleer®) will only be dispensed by pharmacies, practitioners, and health care settings (dispensers) that are certified by Actelion under 505-1(f)(3)(B)
  - "Speak with patient, or their prescriber, every month to obtain confirmation that liver function testing and pregnancy testing was completed"
  - "Obtain confirmation from the patient that the testing was completed"

### How Compliant is UIMC with Bosentan REMS with ETASU?

- Retrospective chart review to evaluate bosentan's usage and appropriate monitoring per REMS with ETASU requirements
- Aims of the study
  - Characterize the patient population at UIMC in which bosentan was used
  - Determine if bosentan was monitored appropriately
  - Based on results, develop a plan of action to improve bosentan's REMS compliance

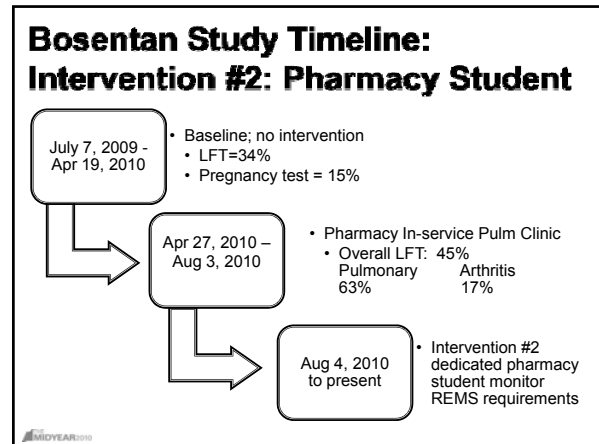
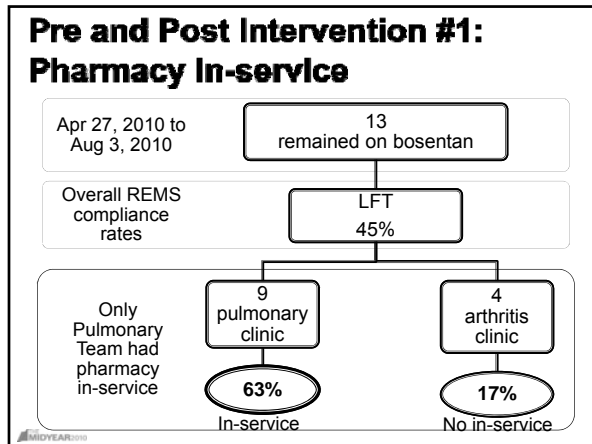
### Bosentan Study Timeline: Review Baseline Compliance Rates

### Baseline Results: Bosentan REMS Compliance Rates\*

All pts prescribed bosentan: N = 19	16 On bosentan	
Labs to be drawn on a monthly basis	LFT	Pregnancy Tests**
Number of actual lab tests drawn	40	6
Number of total lab tests should have been drawn	117	41
REMS Compliance rates	34%	15%

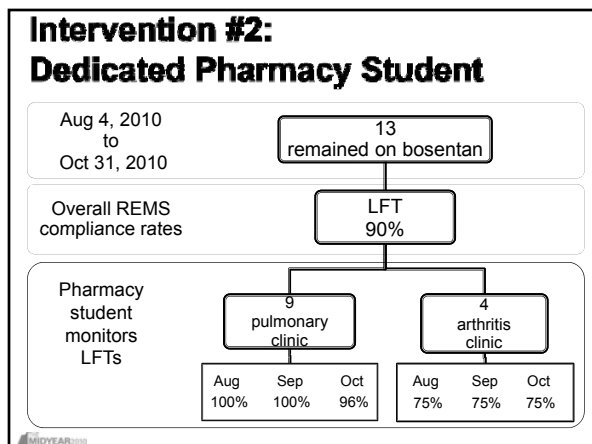
\*Analysis: 1 month before REMS approval (8/7/2009); 7/7/09 to 4/19/10 \*\*Female pts of Child Bearing Potential

### Bosentan Study Timeline: Intervention #1: Pharmacy In-service



- ### Intervention #2 Dedicated Pharmacy Student
- UIC COP Course: 380 Independent Study
    - Overview
      - Student will be undertaking various projects that assist the pharmacist, attending and fellows at a specific clinic
      - Projects may include: quality control audits for high-risk medications and in-service presentations
    - Objectives
      - Understand all medications that are prescribed at each specific specialty clinic
      - Perform literature searches using Medline and PubMed
      - Collect and evaluate data and perform data analysis
      - Complete research training certification including UIC's investigator 101 and HIPAA Research 101 course

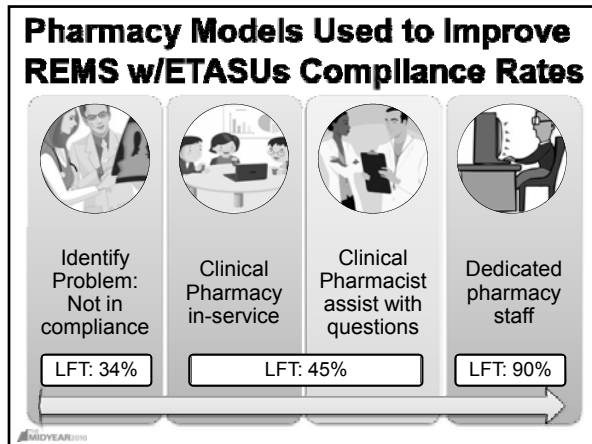
- ### Intervention #2 Dedicated Pharmacy Student
- Student's role in Pulmonary Clinic
    - Follow all patients on bosentan
      - Monitor LFTs and pregnancy tests results
      - Call patients and remind them to have labs done
      - Fill out lab slips and mail to patients
      - Document in EMR (electronic medical record)



### Dedicated Pharmacy Student Monitors REMS Requirements

Time Analysis Study for 2 Month (n=13)

• Call to remind to do lab work	88 minutes
• Review lab results	98 minutes
• Review clinical notes	61 minutes
• Check appointments	45 minutes
• Document in EMR	45 minutes
• Review demographic information	29 minutes
	0 minutes
<b>Total</b>	<b>366 minutes</b>



### Summary

- There are several outpatient medications with REMS with more to come in the near future
- Certified pharmacies may not have direct access to EMR or lab data to confirm compliance
- Institutional pharmacies with direct access to patient records can play an important role in improving REMS compliance

### Summary

- Pharmacy Models
  - Pharmacy in-services
  - Dedicated pharmacy staff
    - Use of pharmacy students: Win-win situation
      - Students learn to interact with patients and medical team early in career and feel they are making a difference in the patients' care
      - The use of pharmacy students to improve REMS compliance allows clinical pharmacists to focus their efforts towards other

Quote from student:

"This independent study course allowed me the opportunity to learn about some of the processes involved in monitoring patients, and it simultaneously provided me with the chance to develop my ability to interact with patients. Furthermore, this course showed me how poor REMS compliance had been prior to the aforementioned interventions. I feel like I can make a significant impact on patient compliance to REMS, and that I can help to show that having someone dedicated to monitoring patients may be valuable in terms of investing or allocating resources"

### Acknowledgements

- Lori Wilken, Pharm.D, CDE, AE-C
- Aishi Chua, Pharm.D Candidate
- Jessica Michaud, Pharm.D, BCPS
- Christopher Lee, Pharm.D Candidate
- Jo Ann Stubbings, BSP Pharm, MHCA

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**EDUCATIONAL SESSION ABSTRACT**  
**2010 ASHP Midyear Clinical Meeting**  
**Anaheim, California**

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**233-5**

**ETASU: Inpatient**

Leonard, M.C.

Cleveland Clinic, Department of Pharmacy/Hb-105, Cleveland, OH 44195, USA.

Email: [leonarm@ccf.org](mailto:leonarm@ccf.org)

The intent of REMS is for the appropriate and safe use of medications. However, some REMS can restrict, delay, or complicate access to medications in hospitalized patients. This can lead to problems with patient care, patient safety, and overall patient satisfaction. Hospital pharmacists need to be able to effectively manage REMS, including educating both health care professionals and patients regarding medication access. In the future, there will be more REMS that affect access to medications in hospitals. Therefore, if an effective system for a REMS program in a hospital is initiated, implemented, and validated, it should be used for other similar REMS programs (i.e., standardization).

**Learning Objectives:**

1. Describe how REMS restricts, delays, and complicates access to medications in hospitalized patients.
2. List methods for handling REMS that restrict, delay, and complicate access to medications in hospitalized patients.
3. Explain the rationale for educating health care professionals, patients, and family members about REMS affecting hospitalized patients.

**Self-Assessment Questions:** (True or False)

1. Based on the SHARE program for vigabatrin, this medication is available from pharmacy wholesalers.
2. In order for a physician to prescribe dofetilide, they must be a certified dofetilide prescriber.
3. Besides giving all patients a Medication Guide, the APPRISE program for ESAs only affects the FDA-approved indication of treatment of anemia due to concurrent chemotherapy in patients with metastatic cancer.

**Answers:** 1 (F); 2. (T); 3. (T)



## ETASU: Inpatient

Mandy C. Leonard, Pharm.D., BCPS  
Asst. Director, Drug Information Services and Formulary Management  
Department of Pharmacy  
Cleveland Clinic

## How REMS Impact Hospitalized Patients

- Restricts access to medications
- Delays access to medications
- Complicates access to medications

## Restricted Access to Medications

- Vigabatrin (Sabril®)
  - FDA-approved for treatment of infantile spasms; refractory complex partial seizures not controlled by usual treatments
  - Boxed warning for vision loss
    - Vision should be assessed to the extent possible at baseline (no later than 4 weeks after initiation), at least every 3 months during therapy and at 3 to 6 months after discontinuation. Once detected, vision loss is not reversible.

## Restricted Access to Medications

- Pediatric patient with infantile spasms is on vigabatrin at home and is emergently admitted to the Cleveland Clinic Children's Hospital

## Restricted Access to Medications

- Per REMS program for vigabatrin (SHARE), Cleveland Clinic inpatient pharmacy cannot obtain medication because
  - 1) Vigabatrin is only available from four select specialty pharmacies in the United States
  - 2) Specialty pharmacy will only send medication to patient's home once all aspects of REMS program for vigabatrin are met

## Restricted Access to Medications

- Patient safety issue if family does not bring in medication from home
- Difficulty in providing the best care to a pediatric patient if inpatient pharmacy cannot obtain the medication
- Stress and burden on family in an already stressful situation

### Restricted Access to Medications

- Discuss with family reason for not being able to obtain vigabatrin
- Request family to bring in vigabatrin from home (travel time and distance)
- Order for patient to “take own medication from home” (policy and procedure)
- Identify vigabatrin (pharmacist)
- Inpatient pharmacies need access to medications

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### Delayed Access to Medications

- Dofetilide (Tikosyn®)
  - FDA-approved for maintenance of normal sinus rhythm in patients with chronic atrial fibrillation/atrial flutter of longer than 1-week duration who have been converted to normal sinus rhythm; conversion of atrial fibrillation and atrial flutter to normal sinus rhythm
- Boxed warning for arrhythmias
  - Must be initiated (or reinitiated) in a setting with continuous monitoring and staff familiar with the recognition and treatment of life-threatening arrhythmias. Patients must be monitored with continuous ECG for a minimum of 3 days, or for a minimum of 12 hours after electrical or pharmacological cardioversion to normal sinus rhythm, whichever is greater.

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### Delayed Access to Medications

- Adult patient with chronic atrial fibrillation is on dofetilide at home and is admitted to the Cleveland Clinic Heart and Vascular Institute

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### Delayed Access to Medications

- Per REMS program for dofetilide, prior to dispensing, it must be verified that the physician/prescriber is a “certified” dofetilide (Tikosyn®) prescriber

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### Delayed Access to Medications

- Delay in patient care because updated list of prescribers may not be readily available to the pharmacist
- Delay in patient care if patient is admitted during night shift because there may not be a “certified” dofetilide (Tikosyn®) prescriber on site
- Challenge to provide best care to patient due to potential lag time in patient receiving the needed medication

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### Delayed Access to Medications

- Pharmacy system (or CPOE system) contains list of “certified” dofetilide (Tikosyn®) prescribers and is updated regularly
- Third shift (“off shifts”) notifies first shift to inform a “certified” dofetilide (Tikosyn®) prescriber to evaluate patient
- Patient misses one dose of dofetilide
- Standard database for certified prescribers for REMS requiring certification/registration

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### Complicated Access to Medications

- Erythropoiesis-Stimulating Agents (ESAs)
  - FDA-approved for treatment of anemia (elevate or maintain red blood cell level and decrease the need for transfusions) associated with chronic renal failure (including patients on dialysis and not on dialysis); treatment of anemia due to concurrent chemotherapy in patients with metastatic cancer (nonmyeloid malignancies)
  - Boxed warning
    - Increased mortality, serious cardiovascular events, thromboembolic events, stroke and increased risk of tumor progression

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### Complicated Access to Medications

- Adult patient is admitted to Cleveland Clinic and needs to have an ESA initiated while hospitalized

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### Complicated Access to Medications

- Per REMS program for ESAs (APPRISE),
  - ESA is dispensed to patients with evidence of other documentation of safe use conditions
- Health care professionals (i.e., prescribers) and "hospital designees" must be specially certified
  - Online certification and enrollment, including APPRISE number
  - Delay in patient care because updated list may not be readily available to the pharmacist
  - Delay in patient care if patient is admitted when there may not be a "certified" prescriber in the hospital

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### Complicated Access to Medications

- Per REMS program for ESAs (APPRISE),
  - Certified health care professional and patient documentation of risk:benefit discussion
    - Paper (ESA APPRISE Oncology Program Patient and Health Care Professional Acknowledgement Form)
    - Signature of prescriber and patient
    - Patient refuses to sign acknowledgement form
  - Maintenance of Acknowledgement Form (random audits)
    - Pharmacist's time to ensure compliance with APPRISE requirements, as well as to manage and maintain required paperwork

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### Complicated Access to Medications

- Pharmacy system (or CPOE system) contains list of "certified" APPRISE prescribers and is updated regularly
- Third shift ("off shifts") notifies first shift to inform a "certified" APPRISE prescriber to evaluate patient
- Inpatient initiation requires discussion between patient and "certified" APPRISE prescriber (signatures on form)
- Hospital designee must maintain required forms (hard copy versus scanned form)

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### Complicated Access to Medications

- Standard database for certified prescribers for REMS requiring certification/registration
- Standard process to maintain and track forms for compliance and potential audits

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### **Complicated Access to Medications**

- Only for cancer patients when ESA used for FDA-approved indication
- Hospital Designee has access to “numbers” for prescribers
- Prescribers must use APPRISE Oncology Program Patient and Health Care Professional Acknowledgement Form
- Electronic Medical Record to maintain completed forms

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### **Conclusions**

- The intent of REMS is for the appropriate and safe use of medications in patients.
- However, select REMS can restrict, delay, or complicate access to medications in hospitalized patients.
- This can lead to problems with patient care, patient safety, and overall patient satisfaction.

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### **Conclusions**

- Hospital pharmacists need to be able to effectively manage REMS, including educating both health care professionals and patients regarding medication access.
- In the future, there will be more REMS that affect access to medications in hospitals.
- Therefore, if an effective system for a REMS program in a hospital is initiated, implemented, and validated, it should be used for other similar REMS programs (i.e., standardization).

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## REMS and EHRs: Impact of REMS on Isotretinoin

Richard A. Wagner, Pharm.D.  
Director, Drug Use Management  
Kaiser Permanente

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## Kaiser Permanente

- Kaiser Permanente is an integrated delivery system (health plan, hospitals, and medical groups)
  - Health care provider
  - Pharmacy provider
  - Purchaser and distributor of pharmaceuticals
- Kaiser Foundation Health Plan, Inc.
- Kaiser Foundation Hospitals
- Permanente Medical Groups

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## Requirements for a REMS

- Statutory language:
  - Section 505-1 of the Act requires the FDA to obtain “input from patients, physicians, pharmacists and other health care providers about how the elements to assure safe use . . . for 1 or more drugs may be standardized so as not to be . . . unduly burdensome on patient access to the drug” and “to the extent practicable, minimize the burden on the health care delivery system.”
  - Periodic evaluation of ETASU programs

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## Impact of Isotretinoin Risk Management Programs

- 2 decades of experience – it is not clear that safety has been improved
- One of the 16 deemed REMS – what can be learned to inform new REMS?
- Example of need to
  - Establish goals through a process involving prescribers and pharmacists
  - Evaluate clinical outcomes rigorously (rate based)
  - Anticipate and track unintended consequences
  - Report outcomes and adjust the quality system

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## Impact of iPledge at Kaiser Permanente

- Journal of the American Academy of Dermatology (accepted, publication pending)
- FDA Public Hearing July, 2010
- Poster ISPOR May, 2010
- Journal of the American Academy of Dermatology: A risk management program aimed at preventing fetal exposure to isotretinoin: A retrospective cohort study. September, 2006

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## Impact of iPledge at Kaiser Permanente

### Study Objective

To analyze the effect of the iPLEDGE program (compared to the SMART program) on rates of fetal exposure to isotretinoin in female patients of child-bearing potential (FCBP).

KPSC IRB Approved

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## Impact of iPledge at Kaiser Permanente

### Methods

- **Data Source**  
The primary data source used in this retrospective cohort study was the linked patient databases at Kaiser Permanente Southern California (KPSC). The patient database contains patient-level data for pharmacy prescription records, laboratory results, and outpatient/inpatient visit procedures and diagnoses. All patient information is linked by a unique patient medical record number.
- **Study Population**  
All females without menopause, oophorectomy, hysterectomy, or ovarian failure.  
Filled at least one prescription for isotretinoin during Mar. 1, 2004 to Feb. 29, 2008.  
At least 10 years of age at the start of a course of therapy.

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## Impact of iPledge at Kaiser Permanente

- In females of child bearing potential
  - There was a total of 4,177 treatment courses in KPSC during our study period
    - note: 2,582 treatment courses during SMART and 1595 treatment courses during iPLEDGE
  - The unadjusted fetal exposure rates increased from 3.10 per 1,000 treatment courses during the SMART program to 3.76 per 1,000 treatment courses during the iPLEDGE program.
  - We used a Poisson regression model for the multivariate analysis
    - Unadjusted risk ratio (RR) = 1.16 (95% CI: 0.93, 1.44)
    - RR Adjusted for age, prior acne medication utilization, prior isotretinoin utilization = 1.09 (95% CI: 0.88, 1.36)

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## Unintended Consequences of iPledge at Kaiser Permanente

- **Prescriptions**
  - In year 1 post iPledge the average number of prescriptions per year for females dropped from 5,125 [before] to 2,793 [after] which is a 46% reduction
  - In year 1 post iPledge the average number of prescriptions per year for males dropped from 5,230 [before] to 3,958 [after] which is a 24% reduction
- **Patients**
  - In year 1 post iPledge the average number of females treated dropped from 2,691 [before] to 1,568 [after] which is a 42% reduction
  - In year 1 post iPledge the average number of males treated dropped from 2,789 [before] to 2,161 [after] which is a 23% reduction
  - Differential impact of iPledge based on age of female patient

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## Issues Regarding REMS with ETASU Programs

- Assessment of evidence and potential for generating evidence that REMS with ETASU have or have not improved patient safety
- Impact on the health care delivery system
- Impact on safety and care delivery from distribution through a central pharmacy system or through chosen Specialty Pharmacy partners
- Consideration of alternative distribution systems to minimize the burden on the health care delivery system

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## Evaluating the Effectiveness of REMS with ETASU Programs

- Monitor and assess the effectiveness of REMS
  - Health care provider input into REMS design
  - Recognize potential conflicts of interest if sponsors are solely responsible to evaluate effectiveness
  - Communication plans assessed by health plans and overseen by FDA
- Assessing the burden on the health care system
  - Seek input from impacted providers, plans and health care systems
- Application of metrics for determining the effectiveness

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**SUPPLEMENTAL HANDOUT**  
**2010 Midyear Clinical Meeting**  
**Anaheim, California**

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**\*\*Materials not provided by presenter in time to meet publication deadline\*\***

**Living with REMS: Case Studies and Best Practices**

**ACPE Activity #204-000-10-233-L04P**

**2.0 Contact Hours / Knowledge-based**

***Moderator:** JoAnn Stubbings, BPharm, MCHA, Manager, Research and Public Policy and Clinical Associate Professor, University of Illinois at Chicago*

**Presentation:**

**Cases and Proposed Changes to REMS**

*Philip E. Johnson, RPh, MS, FASHP*

**Speaker Contact Information:**

Philip E. Johnson, RPh, MS, FASHP

Email: [phil.johnson@moffitt.org](mailto:phil.johnson@moffitt.org)

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**EDUCATIONAL SESSION ABSTRACT**  
**2010 ASHP Midyear Clinical Meeting**  
**Anaheim, California**

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**233-8**

**Future of Pharmacy and REMS**

Hoffman, J.M.

St. Jude Children's Research Hospital, 262 Danny Thomas PL MS 150, Memphis TN 38105, USA. Email: [james.hoffman@stjude.org](mailto:james.hoffman@stjude.org)

Risk evaluation and mitigation strategies (REMS) present challenges and opportunities for health system pharmacists. Pharmacists should proactively plan for the challenges of REMS and leverage the opportunities from REMS. Beyond the implications on pharmacy practice, REMS may have important implications on prescribing patterns and access to various medications, and their implications will differ if the drug is in development or already approved. There is a critical need for improved pharmacovigilance strategies, and REMS are one other tool available to FDA. REMS may provide the FDA greater opportunities to balance access and safety considerations. REMS will continue to grow both in quantity and scope. Key REMS developments to monitor include potential changes in medication guides, introduction of a REMS for certain opioids, REMS for biosimilars, and integration of REMS into the electronic health record. To be successful, REMS must remain focused on patient safety, become more standardized, and all stakeholders must communicate and commit to improving REMS. In their current form, REMS are approximately two years old, and they will continue to evolve and mature. Pharmacists should make positive contributions to REMS maturation.

**Learning Objectives:**

1. Summarize challenges and opportunities from REMS for health-system pharmacists.
2. Describe the future of REMS, including implications for pharmacy practice, the drug approval process, and pharmacovigilance.
3. Identify key developments that will occur in the future as REMS mature.

**Self-Assessment Questions:** (True or False)

1. The FDA states that REMS with Elements to Assure Safe Use (ETASU) are intended to provide safe access to drugs with known serious risks that would otherwise be unavailable.
2. The FDA's authority for REMS will expire within the next year.
3. Proactive plan is necessary for the successful implementation of REMS in health systems.

**Answers:** 1. (T); 2. (F); 3. (T)



## Future of Pharmacy and REMS

James M. Hoffman, PharmD, MS, BCPS  
Medication Outcomes and Safety Officer  
St. Jude Children's Research Hospital, Memphis, TN

## Objectives

- Summarize challenges and opportunities from REMS for health-system pharmacists
- Describe the future of REMS, including implications for pharmacy practice, the drug approval process, and pharmacovigilance
- Identify key developments that will occur in the future as REMS mature

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## CRITICAL Questions

- Is the patient safer because of REMS?
- Are patient outcomes better?
- If not, what can make it better?



## Essential Metrics

- Do REMS decrease patient toxicity?
  - Or do patients receive different drugs?
- Do REMS change prescribing habits?
  - For better or for worse?
- What's the Return on Investment?
  - Do REMS provide value?
  - Or does REMS add cost while detracting from other essential patient care functions (additional cost)?

## Health Systems and REMS – Challenges and Opportunities

- |   |   |
|---|---|
| <ul style="list-style-type: none"><li>▪ Challenges<ul style="list-style-type: none"><li>▪ Increased workload</li><li>▪ Unpredictability and planning challenges</li><li>▪ Information availability</li><li>▪ Education<ul style="list-style-type: none"><li>▪ Patient</li><li>▪ Practitioner</li></ul></li><li>▪ Access</li><li>▪ Continuity of care concerns</li></ul></li></ul> | <ul style="list-style-type: none"><li>▪ Opportunities<ul style="list-style-type: none"><li>▪ Leadership of medication use process</li><li>▪ Education</li><li>▪ REMS facilitate necessary safety discussion</li><li>▪ Pharmacists can be the one to provide solutions</li></ul></li></ul> |
|---|---|

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Stubbings et al. Am. J. Health Syst. Pharm., Sep 2010; 67: 1547 - 1554.

## What is your assessment of the value of REMS?

- No value: REMS do not provide any value and do not improve safety in any way
- Maybe: It depends – REMS are useful in certain situations
- Maybe: REMS are useful, but we need to refine their design and implementation
- Clear value: REMS are a great improvement in drug safety systems

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### REMS and Pharmacy Practice

- Proactive planning is essential
  - Must consider workload and other implications
  - Put REMS in your strategic plan
- Process oriented
  - Build into existing routine care processes
- Formulary system/P&T
  - Facilitates proactive approach that ingrains REMS into routine processes

MIDYEAR2010 Stubbings et al. Am. J. Health Syst. Pharm., Sep 2010; 67: 1547 - 1554.

### REMS: Access and Prescribing Patterns

- REMS and prescribing patterns
  - Do REMS change prescribing patterns?
  - If so, are these changes positive or negative?
- FDA often in a challenging position
  - Obvious tension between:
    - Access vs.
    - Timely approval of new therapies
  - Little tolerance for new safety findings for marketed drugs

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### Compared to 3-5 years ago, what is your opinion on the current appropriateness of ESA use in cancer patients?

- ESAs were overused in the past, and now use is more appropriate.
- ESA use has always been appropriate
- ESAs are now underused
- No knowledge/No opinion/Other

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### REMS: Access and Prescribing Patterns

- Must consider access and use questions from several perspectives
  - Approval process
  - Marketed drug
  - Post-approval safety monitoring

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### REMS can facilitate access to innovative therapies...

- Elements to Assure Safe Use (ETASU)
  - *"Intended to provide safe access to drugs with known serious risks that would otherwise be unavailable"* – FDA REMS guidance
    - FDA makes this determination
    - Other REMS elements not sufficient to mitigate risk
- Examples of innovative products that are on the market today because of REMS

Guidance for Industry Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications. Available at: <http://www.fda.gov/downloads/Drugs/Guidance/Compliance/RegulatoryInformation/Guidances/UCM184729.pdf>. Accessed Nov 1, 2010.

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### REMS: Access and Prescribing Patterns for Marketed Drugs

- REMS are often intended to influence prescribing practices
  - However, it is possible that REMS will influence prescribing practices in a negative manner
- What prompts use of other options?
  - Administrative burden
  - Provider refusal to participate in REMS
- Implications?

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### **REMS: Access and Prescribing Patterns – Post approval safety**

- Critical need for pharmacovigilance
- REMS are another drug safety tool available to FDA
- REMS give FDA more flexibility
  - Compare US and EU rosiglitazone action
  - Do REMS facilitate a better balance between access and safety?

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### **REMS Developments to Watch**

- Growth of REMS
  - Simple quantity
    - Will REMS become the “new normal”?
  - Scope
    - REMS with only a Medication Guide
    - REMS with ETASU
    - Class-wide REMS
    - REMS and frequency of use

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### **REMS Developments to Watch**

- Medication Guides and other changes to Patient Medication information
  - Medication Guide vs. other REMS elements
  - FDA Public meeting in September 2010
- REMS for Opioids
  - Evolving slowly
  - Potential to be the most complex REMS so far

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### **REMS Developments to Watch**

- Data on REMS influence on prescribing patterns and pharmacovigilance
  - As time goes on more data will become available
  - Challenging area of research
- Watch for new applications for REMS
  - Example: REMS have been suggested as an approach to manage overuse of antibiotics?

Antibiotics Need REMS For Public, Not Patient, Safety Reasons, IDSA Says - The Pink Sheet, September 13, 2010

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### **REMS Developments to Watch**

- REMS and Biosimilars
  - Potential for the two to become enmeshed
  - Possible that REMS may facilitate access to biosimilars
- Integration of REMS into Electronic Health Records (EHRs)
  - What are your vendor's plans for REMS?

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### **What is needed for successful REMS?**

- REMS must focus only on patient safety
  - Perhaps this sounds obvious but barriers do exist
  - Keep in mind REMS regulatory structure – FDA holds manufacturer responsible
  - REMS and competition
- Standardization at various levels
  - Standardize actions by type of risk
  - Standardize forms and processes

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### **What is needed for successful REMS?**

- Integration into EHRs
  - Need to move beyond our current paper paradigm
  - Unfortunately, does not appear to be much activity in this area
- Feedback and commitment to improve from FDA and all stakeholders
  - FDA and others clearly engaged
  - What will pharmacists do?

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### **Conclusion**

- REMS are a new drug safety tool and are here to stay
- REMS will continue to evolve and mature
  - REMS are about 2 years old...
  - Do you know any 2 year olds who are always logical?
- REMS represent challenges and opportunities for pharmacists
  - Proactively plan for the challenges
  - Leverage the opportunities

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