The Evolution of REMS

What have we learned and Where are we going?

Meredith Manning, Hogan & Hartson

Rekha Garg, Amgen Inc.

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Disclaimers:

- The comments provided here are solely those of the presenter, Rekha Garg, and are not necessarily reflective of the positions, policies or practices of Amgen Inc.
- Each product and each REMS is unique and requires careful legal and regulatory review and advice

What is a REMS

- Strategy to manage a Serious risk known or suspected associated with a drug
  - Includes specific tools, including labeling (ie, medication guide), communication, and “elements to assure safe use”
  - Effectiveness of the REMS must be assessed on a regular schedule
- Authorized by FDAAA, the REMS statute became effective in March 2008
- Since then, FDA has approved dozens of REMS
  - Only a handful of NME approvals since then have not included a REMS

REMS Approved to Date

- In practice, there are now two types of REMS
  - Labeling and/or Communications-based REMS
    - Medication Guides
    - Dear Healthcare Professional Letters and additional communication efforts only aimed at summarizing the risks
    - Web pages and communication efforts
  - Restricted REMS
    - Include “Elements to Assure Safe Use”
    - May also include restricted distribution, where receipt of the drug is contingent on meeting certain requirements
    - Likely to include Implementation System

Approved REMS*

- 16 Deemed REMS
  - Former RiskMAPs that had some element of restricted use
- 56 Approved REMS
  - 43 REMS with Medication Guides only
  - 13 REMS with more than a Med Guide
    - 8 REMS with Med Guide and Communication Plan
      - Cimzia, Dysport, Effient, Embeda, Forteo, Simponi, Xenazine
    - 6 REMS with Elements to Assure Safe Use
      - Entereg, Letairis, Nplate, Onsolis, Promacta, Sucraid

* Based on FDA website

Required But Not Approval REMS

- ESAs
- TNF-Blockers
- Opioids
- Botulinum Toxin
- Metoclopramide-containing drugs
- CellCept and Myfortic
- Testosterone Gels

REMS Issues: Procedural

- What criteria are applied to determine if a REMS is needed?
  - Certain types of serious risks
  - Abuse risk
  - Minimize off label use
- What criteria to determine if there should be a class REMS or not?
  - Opoids Class REMS but just approved Onsolis REMS (not extended release)
  - Although all TNF blockers identified to have a risk of histoplasmosis, each TNF blocker required a separate REMS and not a class REMS
- What is the best timing to discuss a possibility of REMS with the FDA?
  - At end of phase 2 meeting?
  - At the end of phase 3?
  - In the initial submission?
  - 74 day letter?
  - When and how is OSE involved?
- Do I really need a REMS?

Procedural Issues

- FDA's Backlog
  - Numerous examples of approval delays caused by REMS determinations
  - Numerous examples of approved drugs receiving Information Request Letters for REMS submissions with negotiations extending far beyond six months
  - FDA negotiates, approves, and oversees ALL aspects of the REMS (e.g. enrollment or attestations forms, website, data collection forms, etc)
  - Sponsors need more clarity around this:
    - The process
    - How it works at FDA
    - What will be required and should be expected in terms of the content and format of submissions

Procedural Issues

- Once a REMS is approved, can sponsors make minor or operational changes?
- To date, FDA is requiring prior approval submissions for **ALL** changes
  - The statute includes provisions governing “modifications” to the REMS “strategies”
  - Does this extend to:
    - modifications to enrollment forms designed to make them easier to complete or understand?
    - translations of approved English forms?
    - update to websites to allow e-data entry?
- FDA should adopt a lesser standard for operational changes
  - Such a standard could mirror the “first use” standards applied to promotional labeling
  - The sponsor would risk enforcement action if any change was not “consistent with” the approved REMS
  - Criteria for how to work with FDA to change an approved REMS

Substantive Issues

- Do the statutory tools included as elements to assure safe use work to reduce or manage known or potential risks?
  - Proposed Opioids REMS includes a requirement that each patient review the risks with a registered and trained provider before receiving a prescription
  - But, during the public meeting about a potential class-wide opioids REMS, Dr. Throckmorton questioned the effectiveness of these types of patient acknowledgement forms
  - There is little data to support the idea that patients' will understand the risks, be able to accept those risks within the context of their overall health status, or change their behavior based on those risks
  - Medication guides still not meeting the needs of patients despite 20+ years of research to improve comprehension of risk
- Yet, FDA is requiring:
  - Evaluation of effectiveness of medication guides for all compounds with REMS medications guide
  - Documentation of patient acknowledgement in several large proposed REMS systems prior to receiving the prescription

Substantive Issues

- How will FDA apply REMS to generic drugs?
- The statute requires class-wide REMS for generics that reference drugs with elements to assure safe use
- We are not aware of first-in-class generic approvals for drugs with ETASU
  - Opioids, fentanyl patches, and trentinoin products all pre-dated March 2008
- The recent decision on testosterone gels may be instructive
  - Concerns regarding known risks of secondary skin transfer not adequately controlled by labeling
  - NDA sponsors made labeling changes and instituted Med Guides
  - FDA decided in late August that ANDA applicants must perform secondary skin transfer studies, necessitating 505(b)(2) applications
- The decision could mean that safety concerns will change the landscape for generic drug approvals

Standard Language for Assessment of Medication Guide

- Information needed for assessment of the REMS will include but may not be limited to:
  - A survey of patients' understanding of the serious risks associated with the use of drug X
  - A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
  - A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

Assessment Challenges

- **Survey of Patient Understanding of Serious Risk(s)**
  - Timing of assessment
    - At the time the patient receives the medication guide from the pharmacy?
    - At the time the patient has discussions with the health care provider?
  - Limitations of standard questions across all products
    - Diverse patient population
      - Age, Co-morbidities, Multiple medications
    - Location of where the medication guide is dispensed
      - Retail, clinic, specialty pharmacy, hospital
    - Receipt of the medication guide
      - Patient, caretaker

Assessment Challenges

- **What are we trying to assess?**
  - Did the patient remember receiving the medication guide?
  - Did the patient even know that the information they received is called a medication guide or consumer medication information?
  - Did the patient understand the risks listed in medication guide?
  - Did the patient comprehend the risk listed in the medication guide?
  - Did the patient remember the risk listed in the medication guide without the having the medication guide?
  - Did the medication guide influence patient to make the decision whether or not to take the drug?
  - Who did the patient discuss the medication guide with?
  - Did the caretaker receive the medication guide?

Safety Registries: Adverse Event Collection

- **Minimizing duplication of forms**
  - Spontaneous adverse events already collected by manufacturers
  - Should there be a separate process to collect “pre-defined” adverse events
- **Challenges in collecting data from in clinical practice setting and not clinical trials**
  - Most physicians lack experience in participating in clinical studies
  - No compensation to physicians for time and effort to complete extensive detailed data collections forms
  - Data required on the data collection form not always available in clinical practice
  - Limitation of spontaneous adverse events reported as part of registry compared to clinical trials
  - Inability to change data collection forms in a timely manner

Unresolved REMS Issues

- Prescribers – attestations shift to product liability, interfering with practice of medicine (off label use), requiring physician to discuss the risk and not other health care professionals
- Patient – concerned about privacy (patient's allowing access to medical charts), access to drug only after signing to agree to follow REMS requirement
- Institutions – enrollment, oversight of physician, mandated forms, procedures, costs
- Pharmacies – state vs federal laws, different procedures for each REMS
- All stakeholders
  - Cost of extra time and effort to implement REMS
  - Cost of required monitoring to obtain drug – monthly pregnancy tests, monthly liver enzymes
  - Burden on health care
  - Access to drug

What's Next?

- What Will the REMS Look Like?
- Can FDA balance risk mitigation activities with the existing healthcare system?
  - not overly burden the system
  - should industry alone bear the burden of REMS?
  - Role of consumers and healthcare system
- Consistency and standardization is needed
  - Criteria – certain types of risks - for REMS?
  - Approval and ongoing management of REMS to be sustainable over time?
- Broad stakeholder input is needed