

Morgan Lewis

Regulatory Considerations and Evolving Issues Concerning REMS Programs

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Evolution of Risk Management AT FDA

- 1976 – Patient package inserts (PPIs) required to accompany oral contraceptives
- 1990 – Clozapine “no blood, no drug” restricted access program
- 1998 – System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.TM) restricted access program implemented

Evolution of Risk Management at FDA (cont'd)

- 1999 – Dr. Woodcock issues report entitled *Managing the Risks from Medical Product Use*
- 2004 – Increased congressional attention on post-market drug safety due to adverse events (Vioxx, Bextra, Meridia and Crestor)
- 2005 – FDA releases two guidance documents
 - Describe additional safety monitoring and interventions that may be appropriate for certain products
 - Outline FDA's concept of risk minimization action plans (RiskMaps)

FDAAA and REMS

- New statutory framework to integrate risk evaluation and mitigation into pre-market review and post-market pharmacovigilance
 - Many risk minimization tools in use under the prior law in certain existing drug approvals (e.g., RiskMaps, Subpart H)

FDAAA and REMS (cont'd)

- FDA must determine “that a risk evaluation and mitigation strategy is necessary to ensure that the benefits of the drug involved outweigh the risks of the drug.”
 - Applicable to NDAs, BLAs, ANDAs, and major supplements
- Factors FDA must use to determine need for REMS:
 - Patient population;
 - Seriousness of the disease;
 - Expected benefit;
 - Duration of treatment;
 - Seriousness of known or potential adverse events;
 - Background incidence in the population likely to use the drug; and
 - Whether drug is a new molecular entity

Timing of REMS Requirements

- To date, sponsors typically have learned of the requirement in the context of the Complete Response.
- REMS may be required post-approval if new safety information becomes available

Potential Components of REMS

- FDA has discretion to require one or more of the following elements:
 - A Medication Guide or PPI
 - A risk communication plan; and
 - Use and/or distribution restrictions
- March 22, 2008 – FDA notice deems certain existing drug products with one or more of these components to have an approved REMS
- 55 REMS approved since FDAAA
 - 43 Medication Guide only
 - 6 Medication Guide and communication plans
 - 6 Medication Guide and communication plans and use and/or distribution restrictions

REMS Use and Distribution Restrictions

- FDA may require in the REMS “elements to ensure safe use” of the drug due to toxicity
- To require use and/or distribution restrictions, FDA must determine:
 - The drug can be approved only if such elements are required in the REMS; and
 - Other REMS elements are insufficient to minimize the risk

REMS Use and Distribution Restrictions

(cont'd)

- “Elements to ensure safe use” requirements
 - Specialized training, experience, or certification for prescribing and dispensing healthcare providers
 - Limitations on dispensing from specific healthcare setting (e.g., hospitals)
 - Evidence of certain types of conditions (e.g., lab tests) as a prerequisite to dispensing
 - Monitoring patients taking drug
 - Could include patient registry
 - Could include HCP / pharmacy monitoring

Limitation on “Elements to Ensure Safe Use”

- Elements must:
 - Relate to the specified serious risk identified in labeling
 - Must not be unduly burdensome on patient access
 - Minimize the burden on the healthcare delivery system
 - Compatibility with established distribution, procurement, and dispensing systems
 - Consistent with elements of similar drugs with REMS

REMS Assessments

- Every REMS must include a timeline for submission of assessments
 - Law requires submission at 18 months, 3 years and 7 years
- FDA may discontinue these assessments after the 3-year period if the serious risks of the drug are being adequately managed

Civil Penalties for REMS Violations

- \$250,000 per violation (\$1 million aggregate limit) in single proceeding
- Continuing violations - \$250,000 for first 30-day period (\$1 million aggregate limit for 30-day period)
 - \$10 million limit for all violations adjudicated in single proceeding

Issues with Implementation of REMS

- Currently no guidance on interpretation or on content of REMS submissions
 - FDA to issue two guidance documents: one general and one on content of submissions
 - FDA will need to resolve conflict with other restricted use and distribution restrictions in regulations (e.g., accelerated approval under Subpart H)

Issues with Implementation of REMS (cont'd)

- Industry has expressed desire for increased notice and transparency
 - Ensures equity and consistency
 - Johnson & Johnson and Amgen officials complained that letters giving notice of REMS requirement are vague
 - Difficult to determine where within FDA decision is made, and the standards used in decision-making process

Issues with Implementation of REMS (cont'd)

- Difficult to ensure consistency in REMS requirements and across product classes
 - February 2009: FDA announces requirement for REMS for opioid products
 - July 2009: FDA approves first REMS for opioid products (Onvolis)
 - FDA stated that REMS would be evaluated as case-by-case basis for opioids and that Onvolis is not a model for opioid REMS
 - American Pharmacists Association recently submitted comments to FDA
 - Called for standardized framework to ensure maximum similarity of REMS for ease of implementation

Issues with Implementation of REMS (cont'd)

- FDA needs to establish mechanism to ensure consistency in REMS applications between divisions
 - Will FDA use the Drug Safety and Risk Management Advisory Committee, or will individual advisory committees determine need for REMS?
 - FDA's Pediatric Advisory Committee recommends REMS for Solvay's Androgen to warn of secondary transfer of testosterone gel.
 - If individual committees are used, should a drug safety representative be appointed to each committee?

Issues with Implementation of REMS (cont'd)

- Basis for REMS requirement varies greatly
 - Not just general toxicity concerns
 - Concerns about non-interchangeability among products in same class (e.g., Dysport vs. Botox)
 - Limiting doses to particular contexts (e.g., Entereg limited to 15 in-patient doses)
 - Anti-microbial resistance concerns
 - Drug abuse concerns (e.g., opioids)

Issues with Implementation of REMS (cont'd)

- Will the approval of REMS delay the approval of drugs?
 - Generally, notice is given in the context of Complete Response
 - Can the need for REMS be identified and communicated earlier, e.g., at the pre-NDA meeting?
 - In cases where the need to develop and submit a REMS proposal is the only or predominant deficiency specified in Complete Response, approval is clearly delayed due to REMS
- Will the dispute resolution process be effective and efficient to resolve conflicts regarding REMS?

Issues with Implementation of REMS (cont'd)

- Will REMS affect intellectual property rights?
 - Are REMS programs protected by copyright, as a trade secret, or can they be patented?
- Does FDA have authority to demand information on the intellectual property status (patent or trade secret) of a REMS when it is proposed or make decisions based on the IP status of REMS?

Issues with Implementation of REMS (cont'd)

- Will REMS programs affect competition among products?
 - FDAAA states that restricted distribution programs are not to be used to block or delay generic competition
 - Dr Reddy's filed petition to require brand name manufacturer with restricted distribution program to provide access to drug (at market price) for BE studies
 - Is need for risk management function by sales reps or MSL's too costly for generic manufacturers of products with communication plan or use and distribution restrictions?
 - What if REMS emphasizes non-interchangeability among products?
 - Botox vs. Dysport

Issues Relating to Implementation of REMS Authority

- FDAAA states that generic and brand manufacturers must use a single, shared REMS unless FDA determines that the “burden of creating a shared system” between competitors outweighs the benefit of a shared system
 - What factors does FDA use in this determination?
 - Will FDA hire economists and other experts to assist in such determinations?
 - How much effort must a ANDA holder make to negotiate a license on a proprietary system; what circumstances will cause FDA to waive the elements for safe use?

Issues Relating to Implementation of REMS Authority (cont'd)

- Will REMS programs serve to help the pre-launch promotion of drugs?
 - Could create a buzz surrounding the product
 - Educational/certification requirements require visits by reps/MSLs and force health service providers to pay attention to message
- Will REMS programs affect advertising and promotion?
 - Would omitting REMS information from advertisement be considered misleading, per se?
 - Can reminder ads be used for REMS products, or will they all have black boxes?
 - How do you manage patient chatter around REMS products?

Issues Relating to Implementation of REMS Authority (cont'd)

- Does FDA have the resources to enforce violations of REMS requirement as the number of approved REMS programs increase?
- Might the existence of a REMS program and the associated network with health care providers restrain FDA action when sponsors must address new adverse event information?
 - Biogen's TOUCH restricted distribution REMS program reduced time to develop diagnosis and treatment algorithms for progressive multi-integral leukoencephalopathy (PML)
 - Used TOUCH treatment of the PML side effect in one year, compared to an estimated 3 years without the program

Issues Relating to Implementation of REMS Authority (cont'd)

- Is voluntary reporting of non-compliance a function/requirement of the REMS program?
- How far does liability reach for REMS violations?
 - Extends only to manufacturer?
 - Is manufacturer liable for violations use by healthcare providers?
Is there an auditing duty placed on manufacturers?
 - What authority and penalties exist to deter non-compliance by parties other than manufacturer?

Issues Relating to Implementation of REMS Authority (cont'd)

- Can the REMS authority be managed/implemented to avoid significant adverse economic effects on pharma and the cost of healthcare?
 - Implement the authority to maximize predictability in approach to REMS and timing of decisions for REMS – allows more accurate product valuations and revenue projects
 - Carefully weigh the potential benefits of the REMS against the costs of implementation to patients and providers

Issues Relating to Implementation of REMS Authority (cont'd)

- Will the increased cost of implementation of a REMS program affect the cost of drugs to consumer (i.e., higher co-pays), fees by pharmacists, or reimbursement decisions by insurers?
- Will REMS components be subject to comparative effectiveness analysis?
- Could training/certification programs raise fraud and abuse issues?
- Will REMS affect product liability exposure?

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