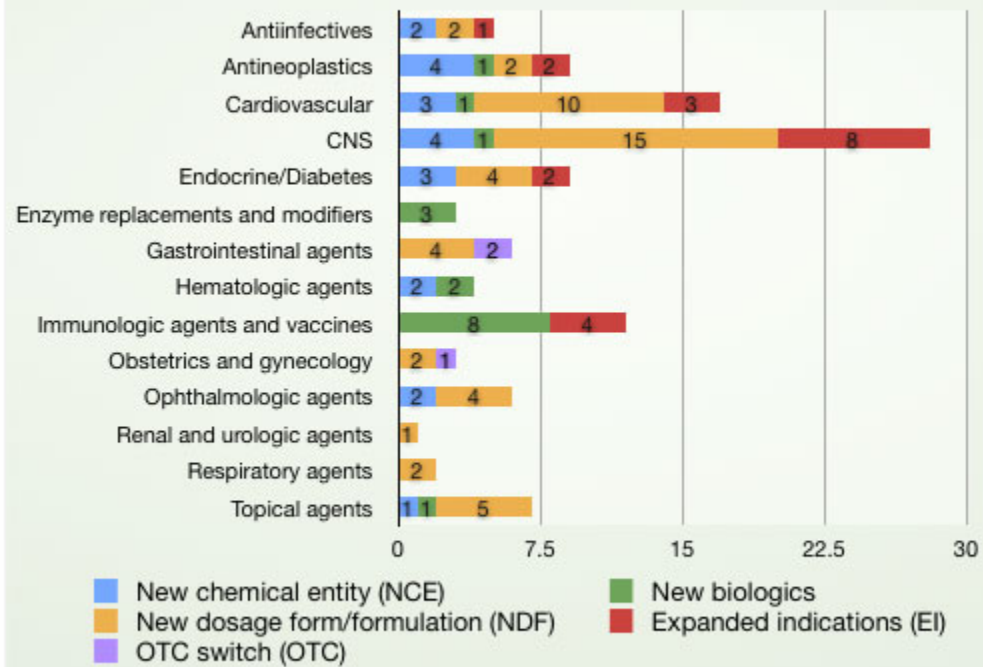


REMS – Can We Mitigate with Restraint?

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Cato Research Washington
June 24, 2010

Approvals in 2009

Significant brand FDA approvals in 2009





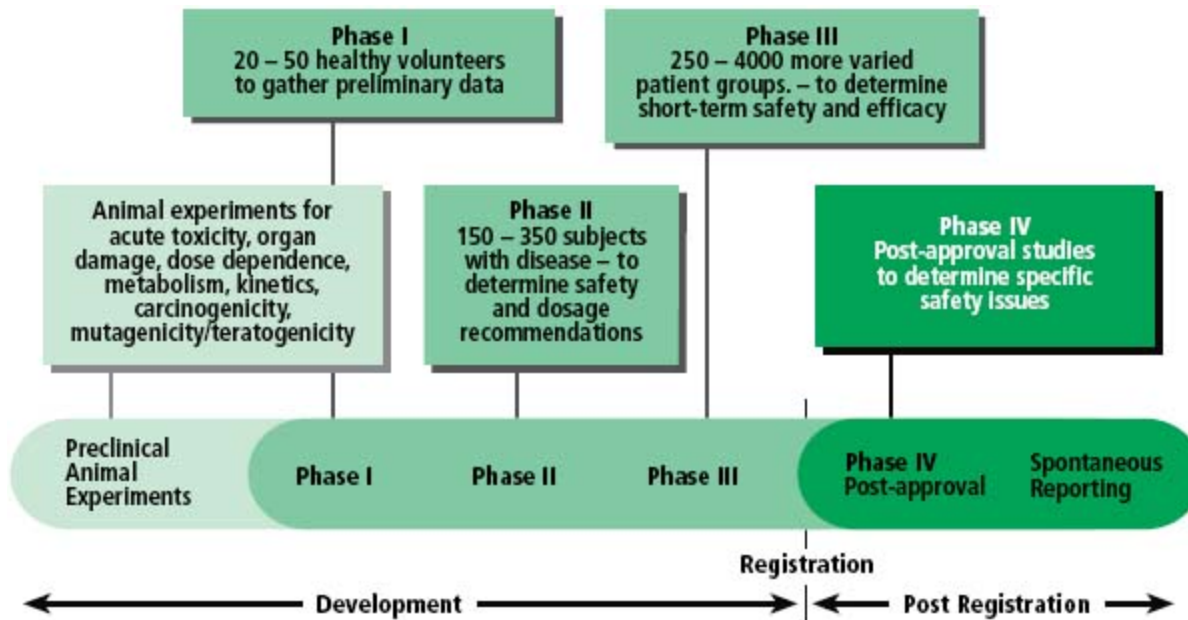
Current Obsession with Safety

- Safety has become the tail wagging the dog!



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Safety at Every Phase!





- Risk Evaluation & Mitigation Strategy

Sharfstein Testimony

March 10, 2010

- “With respect to risk management, if FDA determines that a REMS is necessary to ensure that the benefits of a drug outweigh the risks of the drug, FDA can require manufacturers to have a REMS in place when a drug comes on the market, or implement one later if FDA becomes aware of new safety data . The authority to require REMS provides FDA a very useful set of tools that can be used to reduce the risks of marketed products, while allowing patients to benefit from lifesaving and other beneficial treatments that could not be safely marketed without a risk management program.”

What is a REMS?

- A Risk Evaluation and Mitigation Strategy (REMS) is a required risk management plan that uses tools, as specified in FDAAA, beyond routine professional labeling (the package insert) necessary to ensure that the benefits of a drug outweigh its risks. A REMS is an enforceable document included with the REMS approval letter that describes the elements that an applicant is required to implement.

What is a REMS?

- REMS is defined by the FDA as a program to manage a known or potential serious risk associated with a drug or biologic product. A REMS program may include:
 - Medication guide
 - Communication plan
 - Elements to assure safe use
 - Implementation system
 - Restricted distribution
 - Timetable for assessment

REMS Are Not New

- 16 drugs were approved with restrictive risk management programs before FDAAA (e.g., isotretinoin, thalidomide, mifepristone)
- REMS built on previous experience with risk management programs
- FDAAA clarified FDA's authority to require risk management programs that are enforceable

REMS ≠ “18 month, Ten Thousand Patient Reviews”

- 18-month reviews are mandated under FDAAA (505(r)(2)(D)). Once a drug has been approved for 18-months or has been used by 10,000 patients, whichever is later, a summary analysis of the adverse drug reaction reports received for the drug, including identification of any new risks not previously identified, potential new risks, or known risks reported in unusual number, is performed.

Expanded FDA Authority for Post-Market Safety of Drugs

- Subtitle A – FDA can require:
 - Post-approval studies or CTs from “responsible person” for a “covered app”
 - Inclusion of safety info in labeling
 - Execution of risk evaluation & mitigation strategy (REMS)

Expanded FDA Authority for Post-Market Safety of Drugs

- RP = one who “has submitted a covered app that is pending” or “is holder of approved covered app”
- Covered app = NDA or BLA or ANDA
- Can seek studies “on basis of scientific data deemed appropriate by FDA, including info re chemically- or pharmacologically-related drugs” OR “to ID unexpected serious risk when avail data show potential for risk”

Expanded FDA Authority for Post-Market Safety of Drugs

- Previously app'd covered apps are targets if risk determination based on post-approval safety info
- FDA must show currently required postmarket reports are insufficient to assess or ID risk
- Need timely notice to RP, who must submit timetable for completion & status reports (appeal avail)
- If FDA's new safety info should be in labeling, need prompt notice to RP, who has 30d to submit label supplement or state why label change not needed (FDA must approve/discuss in 30d)

Expanded FDA Authority for Post-Market Safety of Drugs

- From day 15-30, FDA can order compliance
- RP has 15d to comply or 5d to appeal
- After 15d, or 15d from conclusion of appeal, if request not met, RP is in violation of FDC Act.

Risk Evaluation & Mitigation Strategies (REMS)

- “A person may not introduce or deliver for introduction into interstate commerce a new drug if: (i) the product is covered under an approved NDA, ANDA, or BLA; and (ii) a [REMS] is required...with respect to the drug & the person fails to maintain compliance with the requirements of the approved strategy or with other requirements under [§505-1], including requirements re assessments of approved strategies.” 21 U.S.C. §355(p)

Risk Evaluation & Mitigation Strategies (REMS)

- Marketing app can be required to submit proposed REMS if “necessary to ensure that benefits of drug outweigh risks...”
- REMS required for approved covered app if FDA “becomes aware of new safety info and [determines] that [REMS needed] to ensure benefits outweigh risks”

FD&C Act §505-1(a)(1)

- **Pre-approval**, FDA can require a REMS only if agency determines it is “necessary to ensure that the benefits of the drug outweigh the risks of the drug.”

FD&C Act §505-1(a)(2)

- **Post-approval**, FDA can require a REMS only if agency “becomes aware of new safety information and makes a determination that such [REMS] is necessary to ensure that the benefits of the drug outweigh the risks of the drug.”

FD&C Act §505-1(f)(3)

- To mandate elements to assure safe use (**ETASU**), FDA must find that extra measures are needed to “mitigate a specific serious risk listed in the labeling of the drug.”

Sharfstein Testimony

March 10, 2010

- “In the design of REMS with elements to ensure safe use (the most comprehensive REMS programs), FDA is mindful of the provisions in FDAAA stating that the elements to ensure safe use must be, among other things, commensurate with the specific serious risk listed in the FDA-approved labeling of the drug, not be unduly burdensome on patient access to the drug, and be designed to be compatible with established distribution, procurement, and dispensing systems for drugs.”

Risk Evaluation & Mitigation Strategies (REMS)

- To impose a REMS, FDA must consider:
 - Estimated size of pop likely to use product
 - Seriousness of disease/condition to be treated
 - Expected benefit with regard to such disease
 - Expected/actual duration of treatment w/drug
 - Seriousness of known or potential AEs related to product & background incidence of such AEs in population likely to use product
 - Whether product is a new molecular entity

Sharfstein Testimony

March 10, 2010

- “Most of the REMS with elements to ensure safe use include educating prescribers about the risks and appropriate use of the drug as a condition of certification or enrollment in the REMS program. Other programs require enrollment by pharmacists and sometimes patients as well. Some programs require the prescriber to monitor the patient immediately following drug administration and for a period of time afterwards. Each of these programs is designed to provide critical information to clinicians without unduly restricting access to the drugs.”

**SO WHY IS EVERYBODY
SO CONCERNED?**

Why the Concern?

- Will too many REMS (or the wrong kind of REMS) impose added burdens and costs on drug sponsors and on the nation's healthcare system?

Why the Concern?

- Kaiser Permanente filed a citizens petition with FDA in December 2009
- Expressed need for health plans to have a seat at the table when FDA and drug companies discuss REMS design to ensure that these programs don't raise problems for healthcare providers and pharmacies. Requiring consumers to obtain medicines through select doctors or from specialty pharmacies can increase costs for health plans and for consumers and may limit access to needed drugs

Why the Concern?

- Kaiser raised questions about overall benefits of REMS program
- Proposed more transparency in REMS development process by requiring FDA advisory committee review of significant REMS proposals before adoption
- FDA should evaluate established REMS programs at least annually and make these assessments public to help doctors and patients weigh treatment decisions

Why the Concern?

- Pharmacy: Emphasizes need for more uniformity in the structure and requirements of REMS
- ASHP: Recommends standardization of REMS to prevent disruption to patient care
- APhA: Use existing technologies and infrastructure to link REMS to prescriber and pharmacist workflows; any required training for physicians and pharmacists should be coordinated, as should the establishment of patient registries

Why the Concern?

- Ideally, REMS could become an important tool for obtaining more information on drug utilization and outcomes and for detecting drug contamination or diversion, according to a report from the Institute for Alternative Futures on "Optimal Futures for REMS." But to be useful, the program needs standard requirements and uniform methods for REMS design and implementation, especially for restricted distribution systems.

Why the Concern?

- Ultimately, REMS should be linked to electronic medical records, to health plans and programs, and to adverse event surveillance systems in order to bolster the collection of needed information on drug response and clinical effects of treatment for different patient populations.

Concept of Proportionality

- REMS “light” (non-ETASU)
 - Medication Guides
 - “Dear HCP” Letters
 - Focus on “communication”
- REMS “heavy” (ETASU)
 - More infrastructure, more 3rd party involvement
 - May require training and certification of health professionals; limited distribution of the drug to certain healthcare settings; patient monitoring and testing; and enrollment of patients in registries for long-term evaluation

Timetable for Assessment

- Only required element is a timetable for submission of assessments of the REMS
- Required timetable:
 - Assess 18 months, 3 years, and 7 years after REMS approved
 - FDA may specify other shorter frequencies
 - FDA can eliminate assessments after 3 years if determines serious risks of the drug have been adequately identified and assessed and are being adequately managed

Impact of REMS on Third Parties

- 3rd parties includes anyone who isn't a sponsor and who isn't an entity seeking to introduce a drug into ISC
- Some REMS may require sponsor to K with HCP (effectively transferring statutory obligations from sponsor to HCP?)
- E.g., Don't give HCP the drug until s/he Ks to do lab test before prescribing or dispensing drug to patient
- Is the behavior of HCP expected or contracted?

Impact of REMS on Third Parties

- For REMS obligation or expectations of 3rd parties, what must sponsor/FDA do about HCP non-compliance?
- Who collects/records/reports/remedies HCP non-compliance?
- What are consequences of 3rd part non-compliance?

Impact of REMS on Third Parties

- For some designated ETASU, sponsor may be required to “take reasonable steps to...monitor and evaluate implementation of such elements...by health care providers, pharmacists, and other parties in the health care system who are responsible for implementing such elements...and work to improve implementation of such elements by such persons.”

Benefit-Risk Analysis

- Arguably, REMS are reserved only for applications that could not be approved w/o REMS
- Arguably, REMS are reserved only for marketed drugs that would need to be withdrawn unless REMS is adopted
- What if benefits outweigh risks (in the absence of a REMS)? Can FDA seek further “positivity” inside or outside of REMS context?

Benefit-Risk Analysis

- Future role of non-REMS risk management measures, if clearly beneficial but not essential for approval?
- Do we really want a system that *requires* (and therefore encourages) FDA to find a drug to be non-approvable, or subject to withdrawal in order to impose RMCs or RMPs?

Benefit-Risk Analysis

- Should REMS be limited to those designed with ETASU?
- Do we really need to handle perceived needs for Medication Guides *inside* the REMS context?

Risk Evaluation & Mitigation Strategies (REMS)

- REMS must include assessments at 18, 36, 84 mos after approval
- If FDA imposes REMS on effective drug that has serious risks, must post explanation within 30d at website
- Must consider whether REMS will be unduly burdensome on access to drug
- Regs due on how doc can provide REMS product under “expanded access” provisions

Risk Evaluation & Mitigation Strategies (REMS)

- RP can submit assess & mod of REMS anytime
- Assessment required when:
 - applying for new indication
 - part of agreed plan
 - FDA relies on new info
 - FDA issues notice of potential withdrawal of approval

Risk Evaluation & Mitigation Strategies (REMS)

- REMS dispute upon initial approval handled by ADR process
- All other REMS disputes handled by Drug Safety Oversight Board
- Elements reviewable, but not decision to require REMS
- Products approved before 09-27-07 have REMS in effect if have agreement w/FDA re elements to assure safe use or if elements are in effect as required by “accel approval” regs (proposed REMS still due 03-24-08)

Penalties for Violations of FDC Act

§§ 505(o), 505(p), 505-1

- Failure to follow requirements deems a product “misbranded”
- Civil penalties for RP capped at \$250K per violation (\$1M max for all violations in single proceeding)
- If violation continues, RP incurs \$250K for initial 30d period, \$500K for next 30d period, \$1M for each period thereafter, with \$10M cap in any single proceeding

Sharfstein Testimony

March 10, 2010

- “We have learned that designing and implementing the most comprehensive REMS requires a careful balancing of the need to adequately manage risks and also to maintain patient access to important medications. Since using this authority is a work in progress, FDA is committed to addressing the concerns we have heard from prescribers, pharmacists, distributors, and payers about their roles in implementing REMs and from patient groups about the effects of REMS on access to needed products, and are planning to hold a public meeting to hear from these and other stakeholders.”

ACTION ITEMS

Drug-Class or Class-Wide REMS

- Erythropoiesis-stimulating agents (ESAs) used in cancer treatment
- Long-acting Beta-agonists
- Anti-Convulsants
- Anti-Depressants
- Botulinum Toxin Products
- Testosterone Gel Products
- Long-acting opioids (Goal is to decrease abuse and misuse of these high-risk drugs, but it has been difficult to develop meaningful metrics for such behavior and to obtain reliable data on drug-related overdoses or deaths)

BoTox – April 30, 2009

- Citizen petition by Public Citizen Health Research Group
- Covers Botox, Botox Cosmetic, Myobloc, Dysport (not interchangeable)
- Includes MG, CP, Time table for Assessments
- “Offensive REMS” to delay market entry?

Testosterone Gel Products – May 7, 2009

- Covers Androgel 1% and Testim 1%
- Side effects (reversible male precocity) in kids after inadvertent exposure to gels
- Medication guide only
- Class REMS solely intended to reduce risk of a product to a 3rd party and not the patient
- Will FDA impose class-wide REMS to protect people who are not intended to use the product?

Extended Release Oral Opioids

- Opioid manufacturers and other stakeholders will have until October 2010 to comment on what measures to include in risk evaluation and mitigation strategies (REMS) for pain drugs because the FDA reopened the comment period, according to a [notice](#) in the *Federal Register*. The proposed REMS would be applied to prevent abuse and misuse of the products including long-acting and extended-release versions of brand and generic drugs formulated with the following active ingredients: fentanyl, hydromorphone, methadone, morphine, oxycodone and oxymorphone (approximately 25 products, 15 manufacturers).

REMS for Onsolis - July 16, 2009 (fentanyl buccal soluble film)

- MG & CP
- Implementation System
- TTFA
- ETASU
- For opiate-tolerant patients
- Not an Extended-Release Product
- Restrictive distribution
- Enrollment in FOCUS (Full Ongoing Commitment to User Safety) program
- ? Blueprint for inevitable class-wide opioid REMS?

Planning Your REMS

- Consider early planning and preparation of REMS as an “insurance policy” (well before NDA submission?)
- Consider voluntary vs. mandatory REMS
- Consider in-house vs. outsourcing

Planning Your REMS

- Assess the risk profile and anticipate the likely need for a REMS (especially if biologic or specialty drug)
- Any teratogenic, cardiac, hematological, hepatic, or carcinogenic effects? (have triggered REMS)
- Rx of serious or life-threatening disease or Rx for previously unmet medical need? (increased likelihood of REMS)

Planning Your REMS

- What criteria were mandated by FDA?
- Any non-mandated product questions to be answered?
- What countries for inclusion of patients?
- Naïve or experienced physicians & patients?
- How to collect patient data & essential documents?

Planning Your REMS

- What docs/info will need cultural validation and translation?
- Are outcome measures assessed in-office or by phone, paper, or web tools?
- To what extent are patient-reported outcome tools linguistically validated?
- What technologies/expertise can be applied/assembled to reduce costs and create efficiencies?

Assessing REMS Capabilities

- Can you develop and distribute medication guides?
- Can you assess receipt and understanding of medication guides by patients?
- Can you engage physicians, patients, pharmacies, and hospitals?
- Can you manage/oversee ongoing collection of patient data?

Assessing REMS Capabilities

- Can you facilitate integration of REMS and reimbursement programs?
- Can you facilitate appropriately controlled distribution of product?
- Can you assure appropriate reporting of REMS program data to the FDA?

Sharfstein Testimony

March 10, 2010

- “Additional implementation challenges include ensuring consistency in the handling of safety problems with all products, including over-the-counter (OTC) products and generic drugs; the lack of clarity in certain provisions of the law with respect to REMS; and burdens imposed on application holders and FDA that do not contribute significantly to drug safety. We would be very happy to discuss the lessons we have learned over the last two years with Congress and work together to fine tune the program so that it can be even more effective in improving public health.”

Questions for the Future?

- Will FDA intervene appropriately without restricting access?
- How will sponsors determine “reasonable” pre-defined target levels for REMS performance over time?