

Morgan Lewis

Legal Issues Arising from REMS Programs

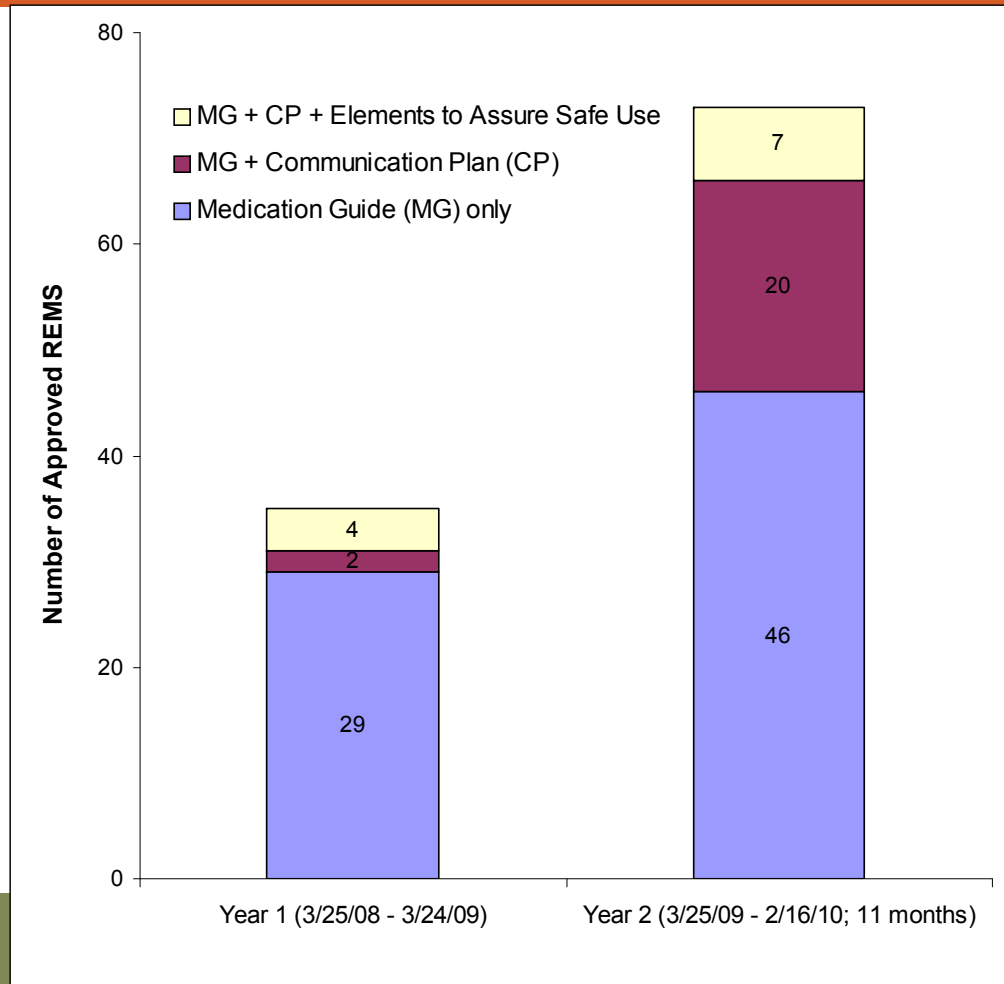
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REMS Under FDAAA

- Section 901 of FDAAA created new section 505-1 of the Federal Food, Drug, and Cosmetic Act (FFDCA), which authorizes FDA to require persons submitting NDAs, ANDAs and BLAs to submit and implement a REMS.
- Giving FDA the ability to require manufacturers to implement REMS has been a “tremendously important authority” and a “milestone legislative achievement.”
- However, Dr. Sharfstein also testified to Congress that FDA needs greater authority to mandate specific REMS programs.
 - Dr. J. Sharfstein, testimony before U.S. House of Representatives, Committee on Energy and Commerce, Subcommittee on Health, FDA Update On Drug Safety, March 10, 2010

FDA-Approved REMS (First Two Years)



Bases for Legal Liability

- REMS authority provides new legal bases for liability and expands regulatory obligations which can trigger liability under already existing legal authorities.
- New REMS authority also allows assessment of civil monetary penalties, which will provide a direct revenue stream to FDA.

Failure Pathways leading to Potential FDA Liability

- Failure to comply with the negotiated system
 - Materials non-compliance (e.g., content, format, scope of materials)
 - Implementation non-compliance (improper or incomplete distribution of materials, incomplete/inaccurate registrations)
 - Monitoring non-compliance (failure to properly monitor/audit system to identify non-complying parties; failure to determine objectives of ETASU are being met)
 - Recordkeeping non-compliance (failure to maintain evidence of compliance)

FDA's New REMS-related Enforcement Authority Under FDAAA

- If a responsible party fails to comply with a requirement of an approved REMS under FDCA section 505-1(d)(timetable), (e)(MedGuide) or (f)(ETASU, including reasonable steps to monitor):
 - The drug is deemed to be misbranded; and
 - The responsible person is subject to a civil monetary penalty.

FDAAA Section 902(a), adding FDCA Section 502(y), 21 U.S.C. 352(y).

- If a responsible party fails to maintain compliance with an approved REMS for an approved drug or other 505-1 requirements, including 505-1(g)(modifying REMS):
 - The person may not introduce or deliver for introduction into interstate commerce this approved drug.

FDAAA Section 901(a), adding FDCA Section 505(p), 21 U.S.C. 355(p).

Existing Statutory Authorities for FDA Enforcement

- FFDCA —
 - 21 U.S.C. §352(y)—misbranded drug and civil monetary penalties;
 - 21 U.S.C. §355(p)—prohibits introduction of drug out of compliance with REMS;
 - §331(a)—prohibits introduction of a misbranded drug;
 - §331(d)-prohibits introduction into interstate commerce of a drug in violation of §505
- Authority to seek injunctions to prevent violations of §331, under 21 U.S.C. §332(a)
- Misdemeanor or felony liability under 21 U.S.C. §333(a)
- Application of *Park* doctrine (strict liability for senior executives) and Responsible Corporate Officer doctrine

Civil Monetary Penalties

- Currently no regulations exist to provide guidance on the circumstances under which FDA will impose CMPs for REMS violations. See however 21 U.S.C. §333(f)(4)(C) (formal evidentiary hearing is available, but no FDA subpoena power) and 21 C.F.R. Part 17 (CMP administrative process regulations).
- FDA may use CDRH device CMP guidance as model—i.e., CMPs are intended to be remedial not punitive, to provide a financial incentive to correct the situation, and should only be used if other remedies are not appropriate, and prior warning given. See Draft Guidance for FDA Staff: Civil Monetary Penalty Policy (June 8, 1999).

Civil Monetary Penalties (cont'd)

- Alternatively, FDA could elect to use the more aggressive HHS model for CMPs used for healthcare fraud in 42 U.S.C. §1320a – 7a
 - Most HHS CMP cases result from self-disclosure of non-criminal type actions.
 - Most are negotiated settlements involving payment of a 5-6 figure penalty.
 - May also be accompanied by type of consent decree.
 - Formal hearing before administrative law judge can be requested, but not used often.
 - Appeal to U.S. federal courts is provided.

Other Statutory Authorities for Enforcement Action on REMS

- Civil False Claims Act, 31 U.S.C. §3729
 - Knowingly causing the submission of false claims for payment by federal health care programs (note — “knowing” can be reckless disregard or deliberate ignorance of the truth or falsity).
 - Typically used by U.S. Attorneys in pharmaceutical off-label cases.
 - Failure to comply with REMS results in a misbranded drug, the promotion of which could result in causing the submission of a false claim.
 - Criminal False Claims Authorities, e.g., 18 U.S.C. 287.
 - Submission of False Statements to FDA, 18 U.S.C. 1001 (knowing submission of false REMS documents or reports to FDA).

Other Possible Enforcement Consequences

- Mandatory or Permissive Exclusion from Federal Health Programs, 42 U.S.C. §1320a - 7?
- Divestiture of product asset(s) improperly marketed?
 - “So one of the things we are exploring right now is saying to drug companies and device companies, that drug that you illegally marketed – you’ve got to divest yourself of it. You have to sell it or you have to waive your exclusivity ...”
 - See Interview of Lewis Morris, Chief Counsel, HHS Office of Inspector General on Nightly Business Report (PBS-TV), March 19, 2010.

Regulatory Mechanisms for FDA Enforcement Action

- Warning Letters
- Applications Integrity Policy (AIP)—invoked where there is a basis to suspect data integrity issues with any submission to FDA
- Inspections/483s
- For imported products, import alerts

Third Party Compliance Issues

- REMS compliance requires implementation of REMS elements by third parties, such as physicians, pharmacies and hospitals:
 - Physicians
 - Reading Dear Doctor letters;
 - Attesting MD has the requisite knowledge and experience; and/or
 - Registering patient in a patient registry when required
 - Reporting incidents of non-compliance.
 - Pharmacists
 - Distributing MedGuides and drugs as required under REMS.
 - Monitoring Patient and MD registries.
 - Distributors
 - Certifications
 - Monitoring

Third Party Compliance Issues (cont'd)

- FDA may use enforcement mechanisms to ensure sponsors “take reasonable steps” to monitor and evaluate REMS implementation.
- What are the “reasonable steps”?
 - FDA draft guidance on REMS content/format (Sep. 2009) provides the following examples of methods used to monitor and evaluate:
 - Certification of wholesalers and/or distributors
 - Maintenance of a validated and secure database of all certified entities (pharmacies, practitioners, and healthcare settings)
 - Conducting periodic audits of pharmacies, practitioners, and healthcare settings
 - Conducting periodic audits of wholesale shipment or distribution systems to determine that the drug is only being distributed to authorized entities if the ETASUs include limits on where and how a drug may be dispensed.
 - Does FDA have authority to require audits? Monitoring and evaluating are much less intrusive.

Third Party Compliance Issues (cont'd)

- Neither FDA nor the sponsor controls or has jurisdiction over the prescribers, pharmacies or hospitals.
- REMS authorization does not require sponsor to conduct pre-program due diligence on MDs who agree to participate in REMS.
- FDA can require a company to decommission an unaffiliated physician/pharmacy or distributor, but could not hold the sponsor responsible unless there was evidence of facilitation of non-compliance.
- If the third party refuses to cooperate for audit or record production, third party likely cannot be forced to cooperate by FDA, although other agencies may become involved, i.e., State Licensing Boards, DEA, etc.
- If a sponsor terminates a distributor or physician from participation, there may be commercial consequences, e.g., state distributor termination laws, inventory return issues, pricing, contract issues.

Sponsor Compliance Issues

- If there is less than 100% REMS compliance:
 - Will FDA exercise enforcement discretion to allow minor revisions to REMS to enhance compliance (so that minor revisions are permitted without FDA's prior approval)?
 - Will FDA only enforce against serious and intentional violations (especially when both FDA and the industry are in a learning curve) or will FDA pursue enforcement against a sponsor for technical or de minimis violations?
 - Will FDA provide sponsors an opportunity to correct before imposing monetary penalties?

See generally, stakeholders' comments on FDA's draft guidance on REMS content/format issued in September 2009 (*e.g.*, Bio, PhRMA comments)

Sponsor Compliance Issues (cont'd)

- Is the company obligated to report all incidents of non-compliance to FDA?
 - Based on FDA draft guidance on REMS content and format, certain reports of non-compliance are expected to be reported to FDA.
 - A proposed REMS should be accompanied by a REMS supporting document, which should contain a REMS Assessment Plan, which should include, among other things, “Report on failures to adhere to distribution and dispensing requirements (by whom?), and corrective actions taken to address noncompliance.” See Draft guidance at line 836-843.
 - Is a violation potentially an Adverse event?
- Is this information public, and do allegedly non-compliant physicians or others have a right to “correct” information submitted about them?
 - Does the physician have a legal basis for action against sponsor for inaccurate information?
- For those companies subject to a CIA, REMS non-compliance may be a reportable event?

Other Regulatory Issues – Promotion

- Downplaying or omitting REMS in promotional materials triggers FDA Warning Letters
 - Gilead: Representative commented that Letairis REMS is only there because of the class – “not that big of a deal.” (FDA Warning Letter 2/27/09).
 - Actelion: Comparative presentation in the flash card misleadingly omits any mention of certain attributes of Tracleer, such as it was deemed to have a REMS, and therefore suggests that Tracleer is a superior therapy. (FDA Warning Letter 11/24/08).

Other Regulatory Issues – HIPAA liability?

- Protection of health information privacy
- Disclosure of PHI by HCP (physician/pharmacist)
- Falls into exception for disclosure of PHI for government mandated information but is consent by patient prudent?
- Will HCPs request Business Associate Agreements from sponsors?
- Penalties for HIPAA violations were substantially increased under the HITECH Act

Product Liability Issues arising from REMS programs

- Sponsors will have access to information that certain prescribers are improperly administering drug products — is communication with the patient allowed, prudent, or required?
- Injured patients may subpoena REMS documents in malpractice actions.

Conclusion—Stay Tuned

- Many unanswered questions concerning FDA's new enforcement authorities involving REMS programs
- The new obligations will cause other government enforcement authorities to consider REMS non-compliance as basis for enforcement action
- There likely will be spill over effect from FDA enforcement actions into private litigation—either commercial or product liability

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