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Let's Be Careful Out There, Says FDA

Pumped with new power, the agency hasn't been shy to order drug makers to minimize risk.

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When the people's representatives talk, the Food and Drug Administration is bound to listen. Last year, Congress became concerned enough about the serious side effects of FDA-approved drugs—think Vioxx and Avandia—to take action. Now the FDA has sweeping new power to require risk mitigation strategies for drugs heading to market or already approved.

And the agency has not been shy about using that power.

Since enactment of the Food and Drug Administration Amendments Act last September, the FDA has assured the industry and the public that it will use its new authority "judiciously" so that the potential burdens on the health system are limited.

But the FDA's actions to date can hardly be described as measured. It has required these new risk mitigation and evaluation strategies (REMS) for fully half of the prescription drugs and biologics approved since the statutory provisions became effective in March. In mid-June, two government advisory committees recommended strict risk management programs for two more drugs. And we are working with several companies with approved products that are currently negotiating these strategies with the agency.

Clearly, the FDA is using its new power to require additional steps to warn of risks—even where those risks are not well defined—and to impose new burdens on manufacturers aimed at managing those risks. In response, manufacturers need to evaluate some key issues left vague in the statute and assess how these issues might affect particular drug products going forward.

Dramatically Different

The FDA's new power allows the agency to require drug manufacturers to adopt REMS to reduce product risks. These REMS can require that drug manufacturers use certain risk minimization tools, require that manufacturers monitor the effectiveness of those tools in addressing particular safety concerns, and allow the FDA to declare the drug misbranded if the tools are not strictly followed.

These new tools arose from Congress' perception of a lack of adequate FDA authority to require drug warnings and control drug distribution. Before the Food and Drug Administration Amendments Act was passed, the FDA had limited power to control drug distribution. After a drug was

approved, the agency could only require sponsors to change the drug's warnings or withdraw approval of the product, a draconian step the agency rarely took.

With this limited power, the FDA had developed a voluntary system under which sponsors would "commit" to implementing risk minimization action plans (known as RiskMAPs) to attempt to address known risks of a drug. But Congress was concerned that the FDA lacked the ability to adequately enforce those voluntary commitments.

Now, with REMS, the FDA can take dramatically different steps beyond those in RiskMAPs. It can require the use of certain risk minimization tools, can monitor their effectiveness, and can oversee the way those tools are used.

Importantly, the FDA may impose a REMS on a product that is under review for initial approval so long as the agency determines that the strategy is necessary to ensure that the benefits of the drug outweigh its risks. In addition, after a drug is approved, the agency may require a REMS on the basis of "new safety information" about a serious risk or unexpected risk from the drug.

A REMS may include three elements: (1) labeling in the form of a medication guide or patient package insert, (2) a communication plan targeted at physicians and patients, and (3) "elements to assure safe use." All REMS must also include periodic assessments of the effectiveness of the strategy after its approval.

The FDA's ability to require "elements to assure safe use" is particularly novel. These may include requiring health care providers who prescribe the drug and pharmacies that dispense the drug to have particular training, expertise, or special certification. They may also restrict use to certain health care settings (such as hospitals), require certain laboratory results or other documentation about the patient before use, subject each patient using the drug to certain monitoring, or require all patients using the drug to be enrolled in a registry.

And because these requirements are novel, they are also subject to substantial uncertainty—in the way that the FDA will interpret the statute, the mandates companies may face in implementing REMS, and the impact REMS may have on the health care system.

What to Watch

Several issues deserve watching for the effects that REMS may have:

• *Orphan drugs.* Drugs intended for use in rare diseases (and correspondingly small patient populations) are routinely approved after study in small numbers of patients. This means that safety issues are difficult to assess before approval.

Consequently, the FDA's Office of Drug Safety and Epidemiology is likely to be wary of approving these products without REMS going forward. In one instance we are aware of, the FDA is requesting that the drug sponsor institute an expansive registry to track patients so that safety information will be captured. Although this is consistent with the purpose of a REMS, it will add substantial costs.

As more of these small-market products are reviewed by the FDA, the agency will have to balance the purpose of the orphan drug amendments (to make these drugs available) with the costs of implementing a REMS. Otherwise, it could become difficult for orphan products to remain financially viable.

• *Restrictions on off-label use.* Although the 2007 statute does not specifically authorize the FDA to consider the potential for off-label use when assessing whether a REMS is necessary, the agency has already done so. When it approved Adolor Pharmaceutical's Entereg (alvimopan), the FDA restricted distribution to hospitals because the agency was concerned that the drug will be used off-label primarily for a condition generally treated in outpatient settings. We are aware of another instance where, during informal discussions, agency officials told a company that it wanted the REMS because of risks presented by off-label use.

The FDA will need to be extremely careful, however, that it not overstep its authority here. When the agency took on the tobacco industry in the 1990s, the Supreme Court rebuked the agency for disregarding clear congressional intent that tobacco not be regulated as a drug. In light of that rebuke, the FDA might want to carefully consider whether it should regulate off-label use through the REMS statute.

• *Medication guides.* Medication guides have been used by the FDA for a decade to warn of risks posed by certain products, and the new statute provides that medication guides may be a REMS tool. The statute also identifies medication guides by referencing the pre-existing regulation—indicating that Congress envisioned that medication guides could exist outside a REMS through operation of the regulation.

When the FDA evaluated RiskMAP programs and "deemed" them as REMS under the statute earlier this year, it did not "deem" all products with medication guides to fall under the REMS authority. Yet, to date, the agency has determined that all products for which a medication guide is approved after implementation of the statute will be regulated under REMS—triggering the assessment requirement. We have confirmed that the FDA was treating all new medication guides as REMS through discussions with agency officials.

This approach signals that the FDA is interpreting its authority expansively. Because medication guides are expensive for manufacturers and require extra effort by distributors, pharmacies, and physicians, the FDA's approach could lead to substantial costs for the health care system.

• *REMS assessments.* The statute provides very little detail regarding the assessments required under a REMS. To date, the FDA has requested that manufacturers assess (1) patient understanding of the drug's risks, (2) distribution of the required labeling, and (3) failures to adhere to distribution and dispensing requirements.

How companies must go about conducting these assess-

ments is unclear because the FDA has not issued guidance regarding the methods or scope of such assessments. Importantly, the results of the assessments may play a key role in whether the manufacturer may be able to negotiate a modification of the REMS.

• *Enforcement.* Failure to comply with a REMS constitutes misbranding under the Food, Drug, and Cosmetic Act. Consequently, companies will need to be vigilant about compliance.

But in addition, the FDA will need to provide some key guidance on how companies should comply because REMS compliance could depend heavily on third-party efforts. For example, the Entereg REMS requires that hospitals "attest" that they have systems in place to assure that the drug will be dispensed only in certain quantities to certain patients. Will the product's manufacturers be held liable should a hospital fail to comply with its attestation? How will manufacturers be expected to monitor providers' actions under a REMS?

Similarly, how will joint ventures and license holders comply? If a holder of a new drug application distributes a drug with a co-marketing partner, will the FDA expect the application holder to audit the partner? If so, manufacturers may need to review license agreements to assess whether the agreements provide adequate monitoring avenues.

These are only some of the myriad of issues that will undoubtedly arise as the FDA implements its new authority. We urge all pharmaceutical and biotech companies to carefully assess their products with the new authority in mind so that they can be adequately prepared should the FDA mandate a REMS for one of their products.

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