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Safety First

How to deal with litigation-related concerns in REMS for biologics.

BIOTECHNOLOGY HAS HAD a profound impact on pharmaceutical development, perhaps most notably in the fields of cancer, diabetes, HIV/AIDS, and autoimmune disorders. Biologics have added major therapeutic options for the treatment of diseases for which effective therapies were either inadequate or nonexistent. As with traditional pharmaceuticals, the Food and

Drug Administration struggles to balance the need for biologics that provide significant benefits to patients against their potential for serious side effects.

Last year's Food and Drug Administration Amendments Act gave the FDA increased authority to require Risk Evaluation and Mitigation Strategies (REMS)—safety plans similar to those previously known as Risk Minimization Action Plans



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(RiskMAP). In-house counsel should be aware of the relationship between REMS and the claims made in a typical failure to warn or omission-based personal injury or consumer fraud litigation.

The FDA's assessment of whether to implement REMS looks to the nature and rate of the potential risk, the size of the population likely to use the product, and the seriousness of the condition to be treated by the product. If the FDA determines that REMS are necessary, the manufacturer can be required to introduce safety measures ranging from additional informational guides to restrictive distribution systems. The FDA expects to issue new guidance for REMS shortly. Until then, the current guidance, "Development and Use of Risk Minimization

TYPES OF REMS

Targeted education and outreach—includes "Dear Health Care Provider" letters, medication guides, continuing education programs, and other methods of educating health care practitioners and patients about the risks and conditions for safe use of the product.

Reminder systems—include patient consent forms, health care training that encompasses testing or other documentation of knowledge, and limitations on the amount of medication dispensed at one time.

These are recommended when targeted education programs are likely to be insufficient to minimize the relevant risk.

Performance-linked access systems—include certification of health care providers and pharmacies and provision of a product to only those patients with evidence of safe-use conditions, such as lab test results. These constitute the most burdensome REMS measures and are only to be considered with unusual risks for which less burdensome systems are likely to be insufficient.

Action Plans,” remains in effect. (See fda.gov/cder/guidance/6358fnl.htm.)

Two biologics represent examples of the REMS spectrum. On the one hand, the medication guide that comes with REMICADE—a biologic that treats debilitating diseases, including rheumatoid arthritis and Crohn’s disease—may look familiar to many in-house counsel. It explains the potential risks of the drug, discusses patients who should avoid the medication, and details other important issues regarding safe use of the product. This program does not interfere with distribution to patients, but highlights the risk information.

At the other end of the spectrum, TYSABRI—a biologic that slows the worsening of disability from relapsing multiple sclerosis—is only available to prescribers and patients enrolled in a restricted distribution system. Developed as a RiskMAP to permit access to a biologic that had been voluntarily pulled from the market after two clinical trial patients developed a rare brain infection, this restrictive distribution program shows how REMS can be used to mitigate and manage even serious risks that are outweighed by the benefits of biologics that treat patients with otherwise limited (or nonexistent) treatment options.

If REMS are needed, identifying and implementing the appropriate measures will involve a substantial amount of internal work by the manufacturer as well as significant interaction with the FDA. Both include opportunities and pitfalls that could have a significant effect on future litigation involving the product. The following are practical considerations for in-house counsel seeking to minimize any negative impact on such litigation and maximize the positive impact.

Don’t be surprised if the REMS process engenders “bad documents” (a paper trail

that casts the company or its products in a bad light). The REMS process may rely on assessments of risk and benefit with which knowledgeable company scientists take issue, and may threaten the business plan for a product. Good people placed under similar stresses often vent, and e-mail is a form of communication that seems to invite heat. Yet—right here at the outset—employees are setting the tone with which the company will have to live. In-house counsel’s attention to e-mail training (and frequent reminders during stressful periods) will be time well spent.

Urge your clients to see this as an opportunity to demonstrate how they can be cooperative with the FDA. Your trial counsel’s ability to later demonstrate to a jury not only that the FDA acted in an authoritative manner regarding the product’s risk but that your company was an active and cooperative participant in that process will go a long way toward convincing a jury that your company should not be held liable for injuries caused by the product. External and, more importantly, internal communications, regulatory submissions, and meeting minutes are just a few examples of opportunities to clearly demonstrate and document the company’s commitment to cooperative participation with the FDA. In-house counsel should review these opportunities with clients.

Review the affirmative story. The FDA guidance regarding the recommended contents of a RiskMAP suggests that the manufacturer describe the risks to be minimized and the benefits to be preserved. Thus, long before a plaintiff’s lawyer has the opportunity to characterize these aspects of the product to a jury, the company can emphasize the important benefits of the product and its impact on patients. Similarly, the manufacturer can emphasize

the more helpful aspects of the risk profile. Is it a rare event? Is there a clear causal relationship or just a suspected association? How does the severity and likelihood of the risk compare to the importance and likelihood of the benefit? Actions taken and statements made prior to litigation carry more weight in the courtroom because they are less likely to be tagged with a litigation-related motive. In-house counsel should give advice and review regulatory submissions with an eye toward how it might look to a jury.

The REMS process may initially seem disruptive, even detrimental. But it is important to keep in mind that it may one day be your best litigation defense. Your need to protect business considerations should be balanced as much as possible with the opportunity to immunize the company from liability. One of the common claims asserted in product litigation is that a manufacturer was aware of and failed to adequately warn about its product’s risk. As the REMS process is specifically designed to increase the warnings to the health care and patient communities, it may constitute a perfect defense against the assertion that the manufacturer failed to provide adequate warnings. Properly handled, this process presents opportunities for in-house counsel to better prepare clients for potential litigation.

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