Trends in FDA’s Use of Class-wide REMS

By William T. Koustas, MS, JD
The Birth of REMS

President George W. Bush signed the Food and Drug Administration Amendments Act (FDAAA) into law on 27 September 2007, a day that people who work on drug regulatory issues celebrate or decry depending upon their point of view. This landmark legislation amended the Federal Food, Drug, and Cosmetic Act (FD&C Act) and the Public Health Service Act. Of the 11 titles that comprise FDAAA, Title IX is the most far-reaching, with provisions intended to improve the postmarket safety of drugs and biologics by granting the US Food and Drug Administration (FDA) the authority to mandate labeling changes, postmarket studies and Risk Evaluation and Mitigation Strategies (REMS).

Under this new power, FDA may require applicants of a New Drug Application (NDA), Biologics License Application (BLA), Abbreviated New Drug Application (ANDA) or a supplement thereof to submit a proposed REMS as part of the application if the agency determines it is “necessary to ensure that the benefits of the drug outweigh the risks of the drug.”4 Further, FDA may require an applicant to implement a REMS after a product’s approval if the 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.”5 A REMS need not be a heavy regulatory burden if it is comprised solely of communication materials (e.g., medication guide, “Dear Doctor” letters, etc.), which drug sponsors were routinely implementing even prior to FDAAA. REMS, however, can be much more onerous if FDA requires elements to assure safe use. Such elements can include healthcare provider certifications and doctor-patient agreements and may be resource intensive to implement. To mandate elements to assure safe use, FDA must find that extra measures are needed to “mitigate a specific serious risk listed in the labeling of the drug.”6 Since Title IX went into effect on 25 March 2008, FDA has required REMS implementation for both new and previously approved drug products.

Implementation of REMS

FDA initially seemed to use restraint in applying the new power bestowed upon it by FDAAA. Douglas C. Throckmorton, MD, deputy director of FDA’s Center for Drug Evaluation and Research (CDER), commented on 27 March 2008 that FDA planned to use its new REMS authority “judiciously,” by “targeted use.”7 Dr. Throckmorton went on to say that “[f]ew REMS [would increase confusion in the system [and] could increase errors and decrease [product] availability.”8 However, as time has passed, the percentage of new products subjected to the requirement for a REMS continues to increase while FDA’s reluctance to impose REMS seems to have dissipated. Within the first year after the enactment of Title IX, FDA approved 31 REMS and is on track to approve 60 to 70 more by the close of year two.6 While most of these REMS consist of less-onerous elements, such as medication guides and communication plans, eight others consist of the more-burdensome elements to assure safe use.7

Initially, these REMS were drug product specific and each was negotiated individually with the NDA, BLA, ANDA or supplement applicant. However, FDA has also been moving toward a practice of requiring REMS for classes of drug products. The most expansive of FDA’s efforts involves opioid drug products, where the agency has held a series of meetings, both public and private, to further develop REMS that will apply to extended-release oral opioid drug products. In addition, FDA has issued class-wide REMS requirements for botulinum toxin-based products, testosterone gel products and TNF blocker products. It is useful to explore a few of the class-wide REMS FDA has imposed thus far in order to better understand how the agency may apply them in the future.

Class-wide REMS for Botulinum Toxin Drug Products

On 30 April 2009, FDA announced that all botulinum toxin products will be required to implement a REMS.8 Interestingly, this decision was announced via a response to a citizen petition filed by Public Citizen Health Research Group (Public Citizen) in January 2008.7 Public Citizen successfully argued that a REMS was necessary for these products as they are associated with a serious risk of botulinum toxin effects spreading from the injection site and causing muscle weakness, loss of bladder control and breathing difficulties, among others.9 The products covered by these REMS are Botox and Botox Cosmetic (botulinum toxin type A), Myobloc (botulinum toxin type B) and Dysport (abobotulinumtoxinA). These products are approved for both therapeutic and cosmetic uses.10

The REMS FDA mandated for these products includes a medication guide, a communication plan and a timetable for assessments, but no elements to assure safe use.11 FDA determined that a medication guide was necessary because botulinum toxin products pose serious and significant public health risks, such as breathing trouble and blurred vision,13 that could affect a patient’s decision to use them. Physicians are required to distribute medication guides to patients at the time the product is administered. In addition, drug sponsors are required to implement a communication plan in the form of a “Dear Health Care Provider” letter describing the risk of botulinum toxin effects spreading from the injection site. The letters must be sent to neurologists, dermatologists and other relevant specialists explaining that botulinum toxin products are not interchangeable.
The manner and timing of FDA’s imposition of this requirement are perhaps more interesting than the REMS itself. FDA had an NDA for a botulinum toxin product under review. The agency made its class-wide REMS determination in response to a third party’s citizen petition and, at the same time, announced approval of the NDA. FDA’s requiring a REMS in response to a citizen petition by a third party could be a prelude to the use of “offensive REMS,” where competitors urge FDA to require a REMS for competitor products in order to delay their entry into the market. Moreover, FDA’s announcing a class-wide REMS upon approval of a product within that class calls into question the ability of other application holders to negotiate the REMS. Though it is possible the sponsors of approved botulinum toxin products informally negotiated their REMS with FDA prior to or in perfect harmony with the user fee clock for the new product, it may be that certain manufacturers are less able to negotiate and were forced to accept REMS developed by others.

Class-wide REMS for Testosterone Gel Drug Products

On 7 May 2009, FDA announced that it would require manufacturers of approved testosterone gel products to implement a REMS. Those products—Androgel 1% and Testim 1%—are indicated for testosterone replacement therapy in men with either a deficiency or absence of endogenous testosterone, and are applied to the upper arms, shoulders or abdomen. Prior to May 2009, the labeling of these products noted that patients should wash their hands after use in order to avoid inadvertent exposure to others.

In December 2008, FDA became aware of eight cases of children who developed serious side effects after inadvertent exposure to testosterone gels. These children, who ranged in age from nine months to five years, experienced “inappropriate enlargement of the genitalia… premature development of pubic hair, advanced bone age, increased libido and aggressive behavior.” The symptoms subsided in most cases once the children were no longer exposed to the products.

In response to several more cases, FDA required the NDA holders of these products to implement a REMS under Section 505-1 of the FD&C Act. The REMS consisted only of a medication guide, which is intended to mitigate the risk of secondary exposure of the gels to women and children. Interestingly, this is a class-wide REMS that is solely intended to reduce the risk of a product to a third party and not the patient. Under Section 505-1, FDA can require a REMS postapproval if it becomes aware of “new safety information” and determines that the REMS is necessary to ensure the benefits outweigh the product’s risks. It is unclear from the language of the statute if a REMS should only be implemented if necessary to reduce risk to the patient, or if it is enough to have a serious risk to a third party. This example may represent another trend in FDA’s use of REMS. FDA may be willing to impose a class-wide REMS to protect people who are not intended to use the product at all.

Class-wide REMS for Extended-Release Oral Opioid Drug Products

In what will likely be the most wide-ranging and extensive use of class-wide REMS to date, FDA announced in a 6 February 2009 letter that it will require manufacturers of certain opioid drug products to implement a standardized REMS for all products of that class. This program will impact an estimated 24 opioid products from at least 16 different manufacturers. FDA has held, and may continue to hold, public and private meetings with stakeholders to develop a REMS program that will meet agency goals of ensuring the “benefits of the [opioid] drugs continue to outweigh the risks.” Opioid drugs affected by this program include both brand-name and generic products that contain fentanyl, hydromorphine, methadone, morphine, oxycodone or oxymorphone. According to FDA, the risks that a class-wide REMS is intended to mitigate are: the use of certain opioid products in patients who are not opioid tolerant; abuse; and accidental and intentional overdose.

The first meeting to focus solely on a class-wide REMS for extended-release opioid products took place on 3 March 2009. This invitation-only meeting was attended by manufacturers and/or sponsors of affected opioid products. FDA discussed its concerns regarding these products and the proposed REMS, and took questions from those who attended. The REMS proposed by FDA at this meeting included a medication guide, elements to assure safe use, an implementation system and a timetable for submission of assessments. FDA noted that the most onerous part of this proposed REMS—the elements to assure safe use—could include healthcare provider certifications, prescriber training, a prescriber-patient agreement and a certification for people dispensing the drugs. Though FDA has yet to confirm the final elements of the REMS it will require for extended-release opioids, it has approved an individual opioid drug product with a substantial REMS. Onsolis (fentanyl buccal soluble film) was approved on 16 July 2009 with a REMS composed of a medication guide, a communication plan, elements to assure safe use, an implementation system and a timetable for submission of assessment. The elements to assure safe use are substantial and include a restrictive distribution scheme that requires prescribers, pharmacies and patients to be enrolled in the Full Ongoing Commitment to User Safety (FOCUS) program. Prescribers and patients must sign an enrollment...
form detailing their responsibilities, while those who dispense the drug must do so via a courier to the patient’s home and not through a retail store.32

While FDA took great pains to stress that Onsolis is not an extended-release drug and is only prescribed to opioid-tolerant patients, the approval of the Onsolis REMS may nonetheless provide clues to the components of the class-wide REMS for extended-release opioid products. FDA further states that the Onsolis REMS is independent of the class-wide REMS associated with the extended-release opioid products.33 Despite FDA’s assurances, one cannot help but look at the Onsolis REMS with an eye toward the class-wide REMS coming in the near future.

Class-wide REMS in the Future

Upon review of FDA’s use of class-wide REMS to date, several things seem clear: the agency’s willingness to impose class-wide REMS has been established; the risk to be mitigated can be a risk to a nonpatient third party; and class-wide REMS range from a mere medication guide to a burden on a nonpatient third party; and class-wide REMS to a nonpatient third party; and class-wide REMS range from a mere medication guide to a burden-some restrictive distribution scheme. Only time will tell if FDA’s use of class-wide REMS will remain relatively limited or if these cases are the wave of the future.

References
1. FD&C Act §505-1(a)(1).
2. FD&C Act §505-1(a)(2).
5. Ibid.
6. FDA has approved 37 more REMS between 25 March 2009 and 16 September 2009, which is a pace of 6.13 REMS per month.
7. There are 16 so-called “deemed” REMS that are outside the scope of this article.
8. In addition to a REMS, FDA announced labeling changes for all botulinum toxin products, including a boxed warning. See FDA Response at 1, Docket No. FDA-2008-P-0061 (30 April 2009) (“FDA Response”).
10. Ibid.
11. For example, Botox is approved for eyelid spams and temporary improvement in the appearance of glabellar lines (frown lines), while Dysport is approved for neck muscle spasms and treatment of frown lines as well. See labels for Botox and Dysport, Myobloc.
12. See FDA Response at 1.
13. Ibid at 17.
14. FD&C Act §505-1(a)(1), (b) (FDAAA contains a schedule for negotiating the language of REMS between the sponsor and FDA).
15. These drugs were also required to include boxed warnings. See Testosterone Gel Safety Concerns Prompt FDA to Require Label Changes, Medication Guide [news release], FDA; 7 May 2009. Available at: www.fda. gov/NewsEvents/Newsroom/PressAnnouncements/ ucm149580.htm.
16. See Androgel 1% and Testim 1% labels (18 September 2009).
17. Ibid.
19. Ibid.
20. It is interesting to consider whether new reports of a known risk are sufficient to meet the threshold requirement of “new safety information” required for REMS of approved products. However, that analysis is beyond the scope of this article.
23. FDA, News Release, Opioid Drugs and Risk Evaluation and Mitigation Strategies (REMS) (6 February 2009).
24. Ibid.
25. Ibid.
27. Ibid.
29. Ibid.
30. FDA Approves Opioid Pain Reliever with Required Risk Reduction Plan [news release]. FDA; 16 July 2009. Available at www.fda.gov/NewsEvents/Newsroom/ PressAnnouncements/ucm172366.htm. (FDA also indicated that it intends to approve similar REMS for Actiq and Fentora in the coming months.).
31. See Onsolis’ REMS. Embeda was another recently approved opioid drug with similar Medication Guidance and communication plan requirements, but not elements to assure safe use. See Embeda’s REMS.
32. See Onsolis’ REMS.
33. Ibid 30.

Author
William T. Koustas, MS, JD is an associate with Hyman, Phelps & McNamara. He holds an MS in biotechnology from the University of Pennsylvania and a JD from American University Washington College of Law. Mr. Koustas can be contacted at wkoustas@hpm.com.

GMP & ISO compliance made easier!

- Over 100 in-stock labels for material and device status
- Custom labels designed and printed in two days
- Label printing software that makes it easy for you to create labels
- SOP templates for procedural compliance with FDA Regulations and ISO standards, ready to be customized to your operations

Free catalog and label samples
Call 800-637-4487 or visit www.gmplabeling.com

GMP Labeling®, Inc.
Granite Bay, CA