A central component of the Food and Drug Administration Amendments Act of 2007 (FDAAA) was enhancing FDA's control and authority over the labeling for prescription drugs and biologics. Section 901(a) of FDAAA added a new Section 505(o)(4) to the Federal Food, Drug, and Cosmetic Act (FDCA), providing authority for FDA to require sponsors to amend the approved labeling for products in response to new safety information. Though it has exercised this authority sparingly to date, FDA's initial implementation of Section 505(o)(4) provides important lessons for how the agency intends to use this key new authority.

How Did FDAAA Affect FDA's Authority Over Drug Labeling?

Prior to enactment of FDAAA, FDA's authority to require sponsors to implement labeling changes was not expressly set forth in the FDCA. Instead, FDA worked cooperatively with sponsors whenever the agency believed that new safety information should be included in the labeling for a product. In practice, the agency's comprehensive authority over the labeling for drug products—including its ability to withdraw the approval of a product—afforded the agency considerable power to mandate labeling changes even before FDAAA. But this authority was exercised on a case-by-case basis, and in a largely unstructured manner. FDAAA, therefore, provided FDA with clear authority to require sponsors to amend labeling and established a streamlined process for discussions between a sponsor and FDA about labeling changes.

Under Section 505(o)(4), if FDA "becomes aware" of "new safety information" that the agency "believes should be included in the labeling of the drug," FDA "shall promptly notify" the sponsor. "New safety information" is defined by...
the statute as information about a serious risk or an unexpected serious risk associated with the use of the drug that FDA has become aware of since the drug was approved, since a risk evaluation and mitigation strategy (REMS) was required, or since the last assessment of an approved REMS. Following notification under Section 505(o)(4), the sponsor has 30 days to either “(i) submit a supplement proposing labeling changes to the approved labeling to reflect the new safety information” or “(ii) notify the [FDA] that . . . the [sponsor] does not believe a labeling change is warranted,” and provide a statement detailing the reasons for that determination. If FDA disagrees with the sponsor’s proposed changes or with its judgment that no labeling change is warranted, FDA may “initiate discussions” with the sponsor “to reach an agreement on whether the labeling for the drug should be modified to reflect the new safety information, and if so, the contents of such labeling changes.” These discussions typically may not extend more than 30 days. Within 15 days of its conclusion, FDA may issue an order directing the sponsor to make “such labeling changes as the [FDA] deems appropriate to address the new safety information.” The sponsor’s only administrative recourse following such an order is to “appeal using dispute resolution procedures” within five days of receiving the order.

If a sponsor fails to submit a supplement or otherwise fails to comply with an FDA order for labeling changes, this may be deemed a violation of Section 505(o)(4) and may subject the sponsor to significant fines and penalties.

How Has Section 505(o)(4) Been Used By FDA?

According to FDA, as of September 2008, the agency had exercised its authority under Section 505(o)(4) on four occasions. First, on April 22, 2008, FDA issued a Section 505(o)(4) notification to manufacturers of erythropoiesis stimulating agents (ESAs) to “require safety related label changes . . . to address the risk of increased mortality and/or poorer tumor outcomes” observed when ESAs are administered to patients receiving treatment for certain cancer types. The Section 505(o)(4) notification was not made public, but FDA later posted a letter reflecting correspondence with one sponsor. In its letter, FDA stated that although the company had responded with a supplement proposing certain labeling changes, further changes were necessary to amend language in the Boxed Warnings, Indications and Usage, and Dosage and Administration sections of its labeling. FDA invoked Section 505(o)(4)(E), directing the company to submit labeling addressing the specific issues FDA identified.

On June 16, 2008, FDA issued its second set of Section 505(o)(4) notifications, this time to sponsors of conventional antipsychotic medications, requiring that they add black box warnings indicating an increased risk of death when used in elderly patients being treated for dementia. The “new safety information” was derived from observational studies suggesting that conventional antipsychotics carried a similar risk to newer products that already carried the warning. An FDA division director commented that “[t]he data we have from observational studies are not ideal, so we struggled with this decision.” Nevertheless, the agency “decided that the data were strong enough to extend the warning to all drugs in this class.” FDA did not release the Section 505(o)(4) notifications, but did announce publicly that the agency was seeking new labeling.

Next, on July 8, 2008, FDA announced that it would require fluoroquinolone antibiotic drugs to carry a black box warning about the elevated risk of tendinitis or tendon injury associated with use of the drugs, and to provide medication guides to patients detailing the medications’ possible side effects. Although warnings about these issues were already included in the labeling of the product, FDA “conducted a new analysis of the available literature and post-marketing adverse event reports.” The agency considered “this new analysis to be ‘new safety information’ as defined in FDAAA” and stated that “it is important to highlight and strengthen information regarding possible side effects . . . because it may affect decisions about the relative risks and benefits associated with these products.” The agency did not release the Section 505(o)(4) notices, but issued

FDAAA, therefore, provided FDA with clear authority to require sponsors to amend labeling and established a streamlined process for discussions between a sponsor and FDA about labeling changes.
a press release disclosing the agency’s intent to seek new labeling.

Finally, on September 4, 2008, FDA issued letters requiring makers of tumor necrosis factor (TNF) alpha blockers to include black box warnings on their labels about the risk of histoplasmosis and other fungal infections. Once again, the warnings and other information about these issues were already in the products’ labeling; FDA’s notification was meant to “further highlight the information about the risk of invasive fungal infections.”

The new warnings appear to have been based solely on spontaneous adverse event reports, and not on any new clinical study or re-analysis of previously reported clinical data. In this situation, the agency issued an “FDA Alert for Health Care Professionals” about the agency’s intent to pursue new warnings.

What Lessons and Questions Arise from FDA’s Initial Use of Section 505(o)(4)?

Although experience with Section 505(o)(4) is limited, the agency’s initial use of this authority raises a host of interesting issues.

Class labeling versus individual product labeling

One notable aspect of FDA’s initial use of its new authority is that the first four Section 505(o)(4) notifications concerned class labeling. All of the notifications were addressed to the manufacturers of certain classes of drugs or biologics: conventional antipsychotic medications, fluoroquinolone antimicrobial drugs, ESAs, and TNF blockers. This early experience suggests that the agency may focus its resources on labeling changes that have a broad impact. Moreover, all of the labeling changes mandated by FDA have focused on black box warnings, suggesting that FDA may use FDAAA primarily for the most serious warnings for drug products.

The type of data needed by FDA to trigger Section 505(o)(4)

The FDAAA definition of “new safety information” encompasses a wide array of data and information. Nevertheless, any warning that FDA requires must be based on sound scientific principles. As FDA has acknowledged, speculative or unsubstantiated warnings can have negative consequences on the public health. Accordingly, even though the statutory definition is broad, it was not clear when FDAAA was enacted if FDA would deploy its new authority to require labeling changes based only on controlled clinical studies or similarly rigorous sources, or if other forms of evidence would be sufficient. Based on these first four instances, it appears that FDA is willing to use its new authority based on a range of data, including observational studies (conventional antipsychotics), a combination of adverse event reports and re-analysis of existing data (fluoroquinolones), or spontaneous adverse event reports alone (TNF blockers). This includes situations in which the data are, at least according to one FDA official, “not ideal.”

Does “new safety information” include information already in the product’s labeling?

Section 505(o)(4) permits FDA to require new labeling if the agency “becomes aware of new safety information” that “should be included” in the labeling of the drug. But several of the initial uses of Section 505(o)(4) addressed information already in the products’ labeling, such as moving existing warnings into black boxes. Thus, it appears that FDA may use FDAAA to require labeling changes even when the information or warning is not truly “new.”

The scope of Section 505(o)(4)

Section 505(o)(4) was enacted to permit FDA to require new safety related warnings for approved drugs and biologics. A question that emerged following enactment of FDAAA was whether FDA would reserve the Section 505(o)(4) process for new or amended warnings, but continue to use preexisting processes for other types of changes, such as changes to indications. Again, initial experience suggests that FDA has taken an expansive view. At least one of the agency’s initial Section 505(o)(4) communications addressed not only the drug’s warnings or precautions, but also language related to indications and dosage.

Public disclosure associated with Section 505(o)(4)

As discussed above, FDA has publicly announced information about each of the first four uses of Section 505(o)(4). The public disclosure mechanisms have varied, including press releases and alerts to health care professionals (TNF blockers, fluoroquinolones), statements to the trade press (conventional antipsychotics), and even public release of correspondence with a sponsor (ESAs). It is not clear what criteria the agency has used to select among these public disclosure mechanisms.

The agency’s initial use of Section 505(o)(4) suggests that FDA has adopted an expansive view of its new authority.
options. It is also remains to be seen whether FDA will release information about prospective labeling changes when only a single product is affected (not class labeling).

Will FDA Provide Additional Guidance on Section 505(o)(4)?

The agency’s initial use of Section 505(o)(4) suggests that FDA has adopted an expansive view of its new authority. But given the complexity of these issues, proactive guidance from the agency on the scope of Section 505(o)(4) and the processes the agency intends to employ would be extremely useful to the regulated community. FDA officials have suggested that the agency is working on guidance addressing Section 505(o)(4), but few details about the scope or goals of the guidance have been offered.18 If guidance is proposed—or even in the absence of guidance—companies may want to provide comments to FDA on how Section 505(o)(4) should be interpreted in light of the statutory scheme, the overall purpose of FDAAA, and the agency’s historical practices. △

3 Id. at § 355-1(b)(3).
4 Id. at § 355(o)(4)(B).
5 Id. at § 355(o)(4)(C).
6 Id. at § 355(o)(4)(D). FDA has authority to extend the discussion period or, if FDA determines that “a labeling change is necessary to protect the public health,” it may accelerate the timelines. Id. at § 355(o)(4)(H).
7 Id. at § 355(o)(4)(E).
8 Id. at § 355(o)(4)(F).
9 See Food and Drug Administration Amendments Act of 2007 (FDAAA) FDA Implementation—One Year After Enactment (September 2008), available at http://www.fda.gov/cdrh/initiatives/advance/fdAAA/ accomplishments.pdf. More recently, agency officials have referred to seven instances in which Section 505(o)(4) has been invoked. See John K. Jenkins, Director, Office of New Drugs, CDER, Remarks at the FDA/CMS Summit: New Drug Review 2008 Update (Dec. 4, 2008).
16 Reinberg, supra note 11.
18 See Industry Unsure About Key Details of FDA’s New Post-Market Powers, FDA Week, Oct. 31, 2008 (“FDA is working on guidance documents to address each of the ‘big three’ post-market elements of FDAAA—REMS, mandatory labeling changes and post-market studies …”).