

Labeling Changes And FDA's Oversight Of Drug Safety

Tuesday, May 13, 2008 --- Enacted on Sept. 27, 2007, the Food and Drug Administration Amendments Act of 2007 (FDAAA) gives the FDA enhanced authorities regarding the post-market safety of drugs.[1]

Such authorities range from requiring post-market studies (phase IV trials) and risk evaluation and mitigation strategies (REMS), to triggering a process to rapidly amend drug product labeling when new safety information comes to light.[2]

The primary post-market drug safety provisions of the FDAAA became effective on March 25, 2008.[3]

Of particular interest are the provisions on safety labeling changes requested by the FDA. Under the Act, if the FDA becomes aware of “new safety information” that it believes “should be included in the labeling of the drug,” then it may trigger a process to rapidly amend the labeling for the product.[4]

This authority is intended to ensure that FDA-initiated labeling changes are made quickly in order to respond to new or emerging safety information about an approved drug.

Since the FDAAA was enacted, there has been a dramatic increase in the FDA’s communication of drug safety information to the public. Indeed, the FDA Commissioner and Deputy Commissioner have recently indicated that “consumers should expect to see more advisories and warnings from the agency about drug-side effects.”[5]

In light of this increase in FDA’s communication of drug safety information, should industry also expect to see a similar increase in FDA requests for safety labeling changes now that the FDAAA provisions have become effective?

The Legal Standard

Under FDA regulations, the so-called Physician Labeling Rule promulgated in 2006, labeling must be revised to include a warning or precaution “about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established.”[6]

This causation standard is more stringent than the mere “association” standard for older drugs, which required only “reasonable evidence of an association of a serious hazard with a drug.”[7]

The FDA has emphasized repeatedly that labeling changes are to be made based on a comprehensive scientific evaluation of the product's risks and benefits according to legal standards set forth in the Agency's regulations, not in response to safety fears that are unfounded.

For example, in the preamble to the Physician Labeling Rule, the agency stated that "labeling that includes theoretical hazards not well-grounded in scientific evidence can cause meaningful risk information to 'lose its significance.'"[8]

The legal standard justifying the FDA to request a drug manufacturer to add a warning or precaution to drug product labeling – "reasonable evidence of a causal association" between the drug and "a clinically significant hazard" – is unchanged by the FDAAA. Nothing in the FDAAA displaced the Physician Labeling Rule or established any other standard.

To the contrary, the FDAAA merely established a process to rapidly amend the labeling of the drug at issue, if the FDA "becomes aware of new safety information that [it] believes should be included in the labeling."[9]

This conclusion is supported by the FDA's recently published proposed rule on supplement applications proposing labeling changes for approved drugs (commonly referred to as "changes being effected supplements" or "CBE supplements").[10]

This proposed rule would require that changes to labeling be based upon "evidence of causal association" that satisfies the causation standard set forth in the Physician Labeling Rule, i.e., "reasonable evidence of a causal association" between the drug and "a clinically significant hazard." [11]

Importantly, the Agency acknowledged in the preamble to the proposed CBE rule that changes to labeling under the new FDAAA drug safety provisions, like CBE changes under the proposed rule, also must satisfy the Physician Labeling Rule's causation standard: "FDA believes that its understanding of [the proposed CBE rule's standard] as reflected in this document is consistent with this enhanced authority [under the FDAAA drug safety provisions] for FDA to control the labeling for drugs and biologics." [12]

Thus, labeling changes – whether sponsor-initiated under CBE regulations or FDA-initiated under the new FDAAA provisions – must be based on reasonable evidence of a causal association between the drug and a clinically significant hazard.

As the Agency itself has said, this uniform standard "ensures that only scientifically justified information is provided in the labeling for an approved product. Exaggeration of risk, or inclusion of speculative or hypothetical risks, could discourage appropriate use of a beneficial drug ... or decrease the usefulness and accessibility of important information by diluting or obscuring it ... [L]abeling that includes theoretical hazards not well-grounded in

scientific evidence can cause meaningful risk information to lose its significance.”[13]

Accordingly, because the legal standard has not changed, and because the policy bases supporting that standard remain valid, and because drugs have not somehow become more dangerous in the months since the FDAAA was enacted, drug manufacturers should not expect a dramatic increase in FDA requests for safety labeling changes. Or should they?

FDA Requests For Labeling Changes

An early indicator of the manner in which the FDA, in practice, may implement the FDAAA’s drug safety labeling provisions may be the case of the erectile dysfunction drugs Cialis, Levitra, and Viagra, and the drug Revatio, used to treat pulmonary arterial hypertension.

These drugs are all members of a drug class known as PDE5 inhibitors. In October 2007, shortly after the FDAAA was enacted, the FDA announced that it had “asked manufacturers of these drugs to revise product labeling after a very small number of patients taking the PDE5 inhibitors reported sudden hearing loss, sometimes accompanied by ringing in the ears and dizziness.”[14]

In doing so, the FDA admitted that “no causal relationship [between PDE5 inhibitors and sudden hearing loss] has been demonstrated,” but it nonetheless determined the limited number of adverse events “warrants revisions to the product labeling for this drug class.”[15]

Indeed, the Agency candidly acknowledged that the absence of relevant data made “it difficult to determine whether these reports are directly related to the use of one of these drugs, an underlying medical condition, or other risk factors for hearing loss, a combination of these factors, or other factors.”[16]

Notwithstanding the absence of reasonable evidence of a causal relationship between PDE5 inhibitors and sudden hearing loss, the manufacturers of these PDE5 inhibitors voluntarily agreed to revise the warning and precaution section of the labels of their drugs.

The FDA’s action on PDE5 inhibitors is not unique. In November 2007, the FDA issued an “early communication” that advised that patients using Chantix, a smoking-cessation drug, had reported side effects including depression and suicidal behavior.

The early communication stated that FDA’s posting of the “information does not mean that FDA has concluded there is a causal relationship between the drug products and the emerging safety issue.”[17]

Pfizer, the manufacturer of Chantix, voluntarily agreed to add warnings to the drug’s labeling, but stated that a “causal relationship between Chantix and these reported symptoms has not been established.”[18]

On Feb. 1, 2008, FDA issued a public health alert about Chantix that said, “it appears increasingly likely that there is an association between Chantix and serious neuropsychiatric symptoms,” and noted that Pfizer had agreed to add a warning to the label.[19]

In a conference call on the Chantix public health alert, the senior FDA doctor on the call was pressed on whether there was reasonable evidence of a causal association between Chantix and increased depression and suicidality, as had been reported by some users of Chantix.

In response, he conceded that, although Pfizer voluntarily agreed to make the labeling change FDA wanted, the legal standard for mandating such a labeling change had not been met.

In response to a question about causation, he stated “that what I meant to say is that it’s certainly possible that these are related. We have no definitive evidence that there is a causal relationship here; it’s just that they are strongly appearing to be related. And as we go further with our review, we may reach a level where we believe that there is clear causality, but we have not gotten there yet.”[20]

Similarly, on March 5, 2008, it was reported that Roche and GlaxoSmithKline (GSK), at the FDA’s urging, had revised the labels of the influenza drugs, Tamiflu and Relenza.[21]

Roche and GSK both revised the warnings and precautions section of Tamiflu and Relenza labels to inform doctors of certain “neuropsychiatric events associated with the use of” the drugs, “in patients with influenza,” that “in some cases result[ed] in fatal outcomes.”[22]

The safety alert issued by FDA, as well as the revised labels, acknowledged that the contribution of the drugs to the neuropsychiatric events “has not been established.”[23]

The impetus for the requested labeling changes were studies of patients in Japan who took Tamiflu and reported experiencing certain neuropsychiatric events, such as delirium, delusions and hallucinations. As FDA regulators conceded, however, delirium and other such neuropsychiatric events can be complications of influenza itself.[24]

Moreover, it appears that the FDA requested changes to the label for Relenza merely because it is in the same class of drugs as Tamiflu, not because of reports of adverse events caused by the use of Relenza (let alone reasonable evidence of a causal association between Relenza and a clinically significant hazard).

Indeed, because Relenza, which is inhaled orally, is not easily absorbed, “experts said the problems probably were related to the influenza rather than the treatment.”[25]

Finally, the reports of adverse events were mostly from Japan, “where Tamiflu and Relenza are used not just to treat influenza but to prevent it, [and] some children are on the drugs for as long as seven weeks. In the United States, the drugs primarily are used to treat illness, and children typically are on them for five days or less.”[26]

Conclusion

It should come as no surprise that, as an institutional matter, the FDA is inclined to err on the side of taking action when it comes to drug safety. After all, the Agency has, in recent years, been subject to withering criticism from Congress and in the media about its handling of drug safety issues.[27]

The new FDAAA drug safety provisions, even though they do not establish a new, less stringent standard for mandating labeling changes, unquestionably reveal Congress’ concern about the FDA’s post-market oversight of drug safety.

As the FDAAA’s new drug safety labeling provisions go into effect, attention should be paid to the way that they are implemented by the FDA. As a matter of law and policy, drug product labeling changes should be based on a comprehensive scientific evaluation of the product’s risks and benefits according to the legal standards set forth in the Agency’s regulations, as the Agency itself has repeatedly argued.[28]

Will the FDA allow political practicalities to prove otherwise? How will the FDA treat companies that resist an FDA “suggestion” to make a labeling change in cases where that “suggestion” does not meet the agency’s own legal standard? Stay tuned.

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[1] See generally Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, tit. IX, 121 Stat. 823 (Sept. 27, 2007).

[2] See *id.* at § 901(a) & (b).

[3] See *id.* at § 909(a).

[4] See *id.* at § 901(a).

[5] Jennifer Corbett Dooren, “FDA to Increase Warnings, Advisories on Side Effects,” *Wall St. J.*, Feb. 29, 2008.

[6] 21 C.F.R. § 201.57(c)(6).

[7] 21 C.F.R. § 201.80(e).

[8] Final Rule, Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3922, 3935 (Jan. 24, 2006) (preamble).

[9] See Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, § 901(a), 121 Stat. 823 (Sept. 27, 2007).

[10] See Proposed Rule, Supplement Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices, 73 Fed. Reg. 2848 (Jan. 16, 2008).

[11] See *id.* at 2853 (cross referencing the Physician Labeling Rule standard at 21 C.F.R. § 201.57(c)(6)).

[12] See *id.* at 2850.

[13] See *id.* at 2851.

[14] FDA, Press Release, FDA Announces Revisions to Labels for Cialis, Levitra and Viagra: Potential risk of sudden hearing loss with ED drugs to be displayed more prominently (Oct. 18, 2007), available at www.fda.gov/bbs/topics/NEWS/2007/NEW01730.html.

[15] *Id.*; see also FDA, Questions and Answers about Viagra, Levitra, Cialis, and Revatio: Possible Sudden Hearing Loss (“Though no causal relationship has been demonstrated, FDA believed that the strong temporal relationship between the use of PDE5 inhibitors and sudden hearing loss in these cases warranted revisions to the product labeling for the drug class.”), available at www.fda.gov/cder/drug/infopage/ed_drugs/QA.htm.

[16] FDA, Index to Drug-Specific Information, Cialis (tadalafil) Information, available at www.fda.gov/cder/drug/infopage/cialis/default.htm.

[17] FDA, Early Communication About an Ongoing Safety Review: Varenicline (marketed as Chantix) (Nov. 20, 2007), available at www.fda.gov/cder/drug/early_comm/varenicline.htm.

[18] Pfizer, Pfizer Statement on Chantix (varenicline) Labeling Update in the United States (Jan. 18, 2008), available at mediaroom.pfizer.com/portal/site/pfizer/index.jsp?ndmViewId=news_view&ne

[19] FDA, Press Release, FDA Issues Public Health Advisory on Chantix: Agency requests that manufacturer add new safety warnings for smoking cessation drug (Feb. 1, 2008), available at www.fda.gov/bbs/topics/NEWS/2008/NEW01788.html.

[20] Transcript of HHS Conference Call, Chantix Public Health Alert (Feb. 1, 2008) (statement of Dr. Bob Rappaport, Director, Division of Anesthesia,

Analgesia, and Rheumatology Products, Center for Drug Evaluation and Research).

[21] Reuters, “2 flu drugs get new warnings,” L.A. Times, Mar. 5, 2008.

[22] FDA, 2008 Safety Alerts for Drugs, Biologics, Medical Devices, and Dietary Supplements (Tamiflu (oseltamivir phosphate)) (available at www.fda.gov/medwatch/safety/2008/safety08.htm#Tamiflu).

[23] Id.

[24] See Christopher Lee, “New Warnings Urged For Flu Drugs’ Labels,” Wash. Post, Nov. 24, 2007, at A2.

[25] Id.

[26] Id.

[27] See, e.g., Anna Wilde Mathews, “FDA Unveils Plan to Boost Oversight Of Drugs Once They Are on Market,” Wall St. J., Feb. 26, 2008 (noting that the FDA has suffered “years of criticism about its handling of medication safety issues”).

[28] In addition to the arguments made by the FDA in the preambles to the Physician Labeling Rule and the proposed CBE Rule that labeling changes are to be made (or not made) according to the legal standards set forth in Agency regulations, see *supra*, the Agency also has made similar arguments in briefs to the U.S. Supreme Court in preemption cases, see, e.g., Brief for the United States as Amicus Curiae at 12-15, *Wyeth v. Levine*, No. 06-1249 (filed Dec. 2007) (arguing that labeling changes mandated by state tort law are preempted by FDA labeling regulations).