

likely not to have understanding of pharmacology or medicine. It is important, therefore, that language for each posting contain facts only, not hypotheses (such as possible mechanisms of action). Such facts should include more context about the emerging safety issue, such as number of reports, the source of those reports in light of the validity of various sources (described above), specific effects on persons with what conditions, etc.

FDA states as an example posting: "FDA is investigating post marketing reports of renal failure in elderly patients treated with Drug A, but a causal relationship has not been established. We are continuing to analyze these reports to determine whether the occurrence of these adverse events affect the risk/benefit assessment of Drug A therapy" (85-88). It is not likely that the patients would understand this sophisticated language. In these brief lines, there are many words or phrases many would not comprehend or even recognize: "post marketing;" "renal;" "causal relationship;" "adverse events;" and "risk/benefit assessment." Language in Drug Watch needs to be written with clarity for comprehension; caution should be taken not to include language hinting at complex statistical relationships (since by the definition of Drug Watch, there are none at the time of the drug posting), or "legalese" language meant to protect the Agency if it errs; the public's health is too important.

Similarly in a second example: "Drug B has been associated with serious skin reactions in patients allergic to eggs (line 100)." The phrase "... has been associated with ..." is not one the public in general will understand. Language must be simplified. In a case like this, something like the following language could be used: "Some people with allergies to eggs have experienced serious skin reactions such as XXX when taking Drug B." To the extent that complex concepts must be presented on a Drug Watch listing, we recommend that each Drug Watch web posting include a link to a well-written, understandable glossary of terms.

Communicating to the Individual

The "average patient" does not exist, so communications from Drug Watch should be crafted carefully to speak to the individual. FDA must be ever mindful that the person reading the Drug Watch web page is not an "average patient," but an individual with unique biological dispositions, varying capacity to comprehend, closely held sovereign beliefs and preferences, and the personal right to act as he or she sees fit on neutral, unbiased information.

We recommend two key principles for Drug Watch to ensure the individual is addressed. First, and foremost, since selection of therapeutic options should be made only within the bounds of the patient-physician relationship where individual biodiversity is best known, Drug Watch should strongly encourage persons affected by a listing of a drug on drug watch to discuss their use of the drug with their physicians. Second, information about an emerging safety issue must contain as much specific data as possible about the persons who have been affected, such as age, gender, locale, whether there were concomitant conditions, whether drug-drug interactions were present, etc. For example, the statement,

“... renal failure in elderly patients ...” (line 85) is insufficient. Specificity will help persons identify whether they personally may be at risk, and will serve to assuage unnecessary fears in those who do not meet the profile. Contextual information is absolutely critical to the safety of persons viewing Drug Watch. We reiterate: Drug Watch should contain no hypotheses that might frighten persons away from taking needed medicines; only facts that help persons relate appropriately to the information.

Drug Watch also should be prepared to meet the needs of individuals for additional information. It is likely that persons affected by a Drug Watch listing (or their physicians) will seek further information from providers, sponsors and FDA. We recommend that for each drug listed on Drug Watch the FDA fund a “hot line” to answer patient questions. FDA also should designate in-house rapporteurs for each listing to communicate effectively with concerned patients and physicians. Drug Watch should contain clear instructions for accessing such support.

Communications to Physicians

Respecting Physicians’ Authority in Practicing Medicine

Healthcare providers, specifically physicians, play an essential role in safeguarding public health and ensuring that a patient is prescribed medication that is appropriate for that individual. Drug Watch can be a powerful tool for healthcare providers by providing the latest information on emerging drug safety issues in a central, easily accessible location.

In order to maximize the effectiveness of this website for physicians and other health care providers, it is essential that the Drug Watch website provide clear, accurate, useful and actionable information that a physician can use as an input in prescribing decisions. However, it is important to realize that the information on the Drug Watch website undoubtedly will be one of many inputs a physician will rely on in treating patients; other information likely used in prescribing decisions would be the medical history of the individual patient, the information contained on the drug label, the physician’s experience with a specific drug, alternative treatment options available, etc. Consequently, it is critical that the FDA ensures that implementation of the Drug Watch website respects physicians’ prescribing discretion and does not infringe on or usurp the physician’s sovereign right to practice medicine. Given that Drug Watch will contain emerging safety information, about which FDA has not yet completed its analysis and about which it has not yet made a decision, it would be inappropriate for Drug Watch to attempt to persuade physicians to alter their medical practice based on Drug Watch. The purpose of Drug Watch should be to inform choice rather than to persuade.¹⁴ To that end, Drug Watch should not advise patients or practitioners to discontinue prescriptions, and FDA must act with caution in advising physicians how to respond to information on the Drug Watch website.

¹⁴ Ellen Peters (in press).

Furthermore, Drug Watch should make clear that the drug label remains the definitive document for purposes of the practice of medical care; the information contained in the label reflects careful evaluation of a drug's risks and benefits, while the information on Drug Watch reflects emerging information that the FDA is continuing to evaluate. As a result of the preliminary and inconclusive nature of the information on Drug Watch, FDA must ensure physicians understand that information contained on Drug Watch represents only additional information to consider and is not meant to supplant the information contained in the drug label. This is critical since the information on the Drug Watch website may not necessarily be consistent with the approved labeling of a drug. This inconsistency may, over the long term, erode the value of the label as the "definitive" product document, thereby depriving physicians of one definitive source to turn to for prescribing information. If physicians attempt to turn to a drug company's sales representatives to answer questions regarding this inconsistency, the sales representatives likely will be unable to clear up any confusion since they are constrained from discussing information that is not contained in the product label.

Providing Needed Information

In all instances, Drug Watch should provide fact-based information, as well as an assessment of the quality of the evidence surrounding emerging safety information. Providing such contextual information is important since as the Drug Watch guidance indicates, the "posting of information on the Drug Watch Web page does not mean that the FDA has concluded there is a causal relationship between the product and the risks or adverse events described" (lines 137-139) nor does it "mean the FDA is advising practitioners to discontinue prescribing the products that appear on the Drug Watch" (lines 139-140). Given these statements, it may be unclear to physicians how they should interpret Drug Watch postings, particularly in cases where the FDA has not evaluated the significance of the information.

This lack of clarity is exacerbated when the information posted for a drug does not contain the specificity necessary for judging how a risk may pertain to an individual patient. For example, the sample drug posting provided in the guidance (lines 85-88) fails to indicate how "elderly" is defined. It also fails to identify whether the risks potentially are linked to drug-drug interactions or other factors. Additionally, it neglects to provide a projected date for when the FDA's analysis of the risk signal is likely to be completed. Without more detailed information on the potential safety information, it is unlikely that physicians will know how to make use of the Drug Watch data in their treatment of individual patients.

Ensuring Timely Communication

It is extremely important for FDA to communicate clearly, frequently and accurately to physicians regarding Drug Watch, especially given that consumers will have access to the web site and may turn first to their personal physician for answers on how postings may affect them as individual patients. To that end, it is important for each posting on Drug Watch to list a point of contact at FDA with whom a physician may consult for more

information about a specific drug's potential safety risks. This is particularly critical during the interval in which the FDA considers the risk information as emerging and is still evaluating its relevance.

Communicating to Media

Many persons will initially hear about a new Drug Watch listing through the media. As FDA is well aware, the number of adverse event reports usually increases with media attention, thereby giving the impression that a safety issue is even more serious. We recommend that FDA plan ahead how it will deal with the media attention a new posting will garner, in order to dampen the social amplification of risk.

Communications About Entrepreneurial Use

As we believe the Agency has correctly pointed out, the listing of a drug on Drug Watch is not to be taken as an opportunity for competitor manufacturers whose similar drug is not on Drug Watch to improve marketing of its drug; nor is it to be diminished by the sponsor manufacturer in order to diminish the import of the potential safety issue. We strongly support this stance. Such practices would have the effect of implying a difference for which neither sponsor nor competitor drug is labeled. We recommend that FDA should enhance its vigilance on such false labeling, real or implied, and bring to bear against violators of this rule the full weight and force of its office. Each posting on Drug Watch should contain a strongly worded prohibition against entrepreneurial use, including inappropriate detailing. It also might be useful to have a statement on each Drug Watch listing that explicitly states to health care practitioners and patients that any company claiming that its product is safer than those appearing on Drug Watch is providing misleading information. We recommend that FDA include such a statement, along with a reminder to patients that they should not discontinue or switch any medication without further consulting their physician.

Accountability for Communications

FDA is taking a big step by reporting "emerging" information to the public without having a clear idea of how patients and doctors are likely to respond to such information. Anecdotal evidence on reactions to media coverage of alleged safety issues for certain drugs or drug classes (e.g., SSRIs) indicates that some patients become confused, afraid and stop taking needed medicines, and some doctors become frustrated and angry, not certain how to respond on behalf of their patients. We strongly recommend that FDA regularly monitor and evaluate the impact of communications on Drug Watch on patient and physician behavior, then modify communications appropriately so that patients are not unnecessarily frightened and physicians are not confused. We suggest that FDA use outside experts in medicine, psychology and risk communication to help it accomplish this crucial task.

Procedural Issues

Notwithstanding the above remarks, we believe there may be an issue with respect to whether FDA has the legal authority to adopt Drug Watch in the manner proposed. Section 705 of the Federal Food, Drug and Cosmetic Act (“FDCA”), 21 U.S.C. § 375, as well as the text and structure of the FDCA, suggest that FDA may be precluded from communicating unsubstantiated drug risk information as proposed in the draft Guidance. FDA has not addressed its legal authority in the draft Guidance and we believe it is important for it to do so.

At a minimum, however, a program such as Drug Watch must be adopted by FDA pursuant to notice- and- comment rulemaking under the Administrative Procedure Act (“APA”). Drug Watch constitutes a change in FDA’s existing rules for addressing emerging risk information. Under settled principles of administrative law, agency action that effectively amends a previously adopted regulation, or that amends an agency’s interpretation of a previously adopted regulation, triggers the APA requirement of notice-and-comment rulemaking. *See Alaska Prof. Hunters Ass’n, Inc. v. FAA*, 177 F.3d 1030, 1034 (D.C. Cir. 1999) (“When an agency has given its regulation a definitive interpretation, and later significantly revises that interpretation, the agency has in effect amended its rule, something it may not accomplish without notice and comment.”). Here, FDA has said that, although it “has long provided information on drug risks and benefits to healthcare professional and patients . . . when we were certain of its significance or it prompted a regulatory action,” the agency would henceforth “make important drug safety information available to health care professionals and patients” through the Drug Watch. 70 Fed. Reg. 24,606, 24,606 (May 10, 2005). The Agency may only lawfully accomplish this after notice-and-comment rulemaking.

Even if the Drug Watch does not effectively amend an agency regulation or interpretation, the program constitutes a legislative rule that can be issued only through notice-and-comment rulemaking. An agency may establish a binding norm with legal consequences for private parties or the agency only if it first follows these procedures. *See Croplife Am. v. EPA*, 329 F.3d 876, 883 (D.C. Cir. 2003) (a directive announced in a press release constitutes a substantive rule, for which notice-and-comment rulemaking is required, because it binds private parties or the agency itself with the force of law); *General Elec. Co. v. EPA*, 290 F.3d 377, 382-83 (D.C. Cir. 2002) (a “guidance” is a legislative rule because it purports to bind regulated entities and the agency); *see also Appalachian Power Co. v. EPA*, 208 F.3d 1015, 1024 (D.C. Cir. 2000) (a guidance establishing a new regulatory regime constitutes a legislative rule for which notice-and-comment rulemaking is required). The draft Guidance commits FDA to specific actions and has profound consequences for regulated entities by changing the circumstances under which data they turn over to the Agency will be disclosed, with dramatic product liability and commercial implications. This is precisely the type of agency action that requires compliance with notice-and-comment rulemaking. The draft Guidance alters FDA’s well-established regulatory regime for the dissemination of risk information. Accordingly, FDA may not lawfully adopt the Drug Watch through the publication of a Guidance Document.