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Division of Dockets Management (HFA-305)
Food and Drug Administration
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Rockville, MD 20852

Re: Comments of the Biotechnology Industry Organization on FDA's Draft Guidance "FDA's "Drug Watch" for Emerging Drug Safety Information," Docket 2005D-0062 (*Federal Register* Vol. 70, No. 89, May 10, 2005)

Dear Madam/Sir:

I. Introduction

The Biotechnology Industry Organization (BIO) appreciates the opportunity to provide comments on the Food and Drug Administration's (FDA's) Draft Guidance, "FDA's 'Drug Watch' for Emerging Drug Safety Information," the notice of availability (NOA) for which was published in the *Federal Register* on May 10, 2005 (70 Fed. Reg. 24,606). BIO represents more than 1,000 biotechnology companies, academic institutions, state biotechnology centers, and related organizations in all 50 U.S. States and 33 other nations. BIO members are involved in the research and development of healthcare, agricultural, industrial, and environmental biotechnology products.

The biotechnology industry has developed more than 200 drugs and vaccines that have helped millions of people worldwide. These products have had a powerful impact on conditions such as multiple sclerosis, rheumatoid arthritis, genetic disorders, heart attacks and strokes, cancer, and many others. Biotech companies are developing two-thirds of the drugs in the pipeline for rare diseases, and are developing products for conditions prevalent in the third world such as malaria, tuberculosis and HIV/AIDS. These

innovative biological products are intended for use in the diagnosis, prevention, and treatment of disease and are, therefore, regulated by FDA.

Medicines must not only be effective, but also safe – and biotechnology offers new ways to produce safer treatments with fewer side-effects. Pharmacogenomics, for example, is providing more and more information about the ways drugs work differently in different people. This offers an opportunity for biotechnology researchers to better determine when products in development will present safety issues and develop targeted approaches to minimize adverse effects. Pharmacogenomics also offers the promise that post-approval, physicians and patients will have more information about the type and dose of medication that are likely to work best for a patient, given a particular genetic and environmental profile.

However, it is important to note that "[a]ll drugs have risks," as FDA observed in the NOA. FDA's system for premarket review and approval of products is widely considered to be the world's "gold standard." Nevertheless, there is always a possibility that a safety issue is so rare – or sometimes so common – that some questions may not emerge until after approval. Testing a product in pre-market clinical trials cannot universally assure that we know how a product will perform in the general population once approved. For this reason it's essential that strong post-approval drug safety programs be in place to supplement FDA's strong pre-approval review processes; consumers deserve no less. Information about risks that arise following approval must be conveyed to prescribers, and this information must be up-to-date and authoritative so that prescribers can continue to engage in appropriate risk management in clinical practice.

Effective postmarketing risk communication is perhaps more important today than ever before. Patients are increasingly involved in their own health care. They rightly expect access to comprehensive information about available therapies. An unprecedented amount of such information is available through the Internet and from other diffuse sources. Too much of this information is outdated, incomplete, or incorrect. BIO is keenly interested in methods to improve the quality of information available to patients about therapeutic products.

BIO therefore fully endorses the notion, articulated by FDA in the NOA, that "patients and healthcare professionals [should] have quick access to the most up-to-date and accurate product information available in an easily accessible form." However, BIO has serious concerns about whether the Draft Guidance will afford access to up-to-date and accurate product information. We also have significant concerns regarding the inconsistencies between the Draft Guidance and the current comprehensive system for the dissemination of information about prescription drug risks to the public, as set forth in the Food, Drug and Cosmetic Act (FDCA), 21 U.S.C. §§ 301 et seq.. In Section IIIA of these comments we explore these concerns more fully, and we state our position that the APA prohibits FDA from altering the existing system to the extent provided by the Draft Guidance without engaging in notice-and-comment rulemaking.

In the event FDA were to decide to go forward with Drug Watch in some form, we make specific suggestions about how it should be modified to better serve the public health. We suggest four major areas for improvement:

1. BIO is concerned that the site may not be as helpful to patients and providers as it could be, and may actually negatively impact the public health, unless issues are resolved such as use of potentially unreliable data, inconsistent standards of evidence, inconsistencies with manufacturer's terminology, conflicting standards or goals about how information on the site should be used, and ambiguity about how consumers should react in the face of incomplete information. In addition, the Draft Guidance is not explicit about the type of information the web site will include, and it does not set a clear threshold for posting information.

   The credibility of the site will be essential for it to be a meaningful, reliable benefit for patients. As FDA explained in its seminal report, Managing the Risks From Medical Product Use (May 1999) (Part 1), "FDA's role in reducing risk involves ensuring that accurate, substantiated, and balanced information about a product is available to the prescriber and the patient." BIO believes that at a minimum, information posted to the site must be determined by FDA to be scientifically valid, peer-reviewed, and clinically meaningful (hereinafter described as "supported by substantiated evidence") and comprehensible to patients and providers.

2. We are further concerned about the potential for a negative impact on patients' health that could result from their obtaining "false positive" information from the web site, i.e., information that suggests a risk when one does not exist. We recognize that FDA intends to provide strong and clear encouragement for patients to see their providers before, for example, discontinuing a medication, changing dosage, or changing to another treatment with different risks. However, not all consumers will heed this advice, and these consumers could be harmed by acting on information that has not been evaluated thoroughly.

3. We note that the Draft Guidance does not include a discussion of the potential for products liability and/or medical malpractice claims that could arise from either the publication of certain information on the site, or from physicians acting on information that subsequently is determined to be inaccurate. It is important that consideration be given to the critical implications of, and consequences from, FDA's actions. Preliminary and inaccurate information, or information that can lend itself to misinterpretation, can have a devastating effect on innovative biotechnology companies in terms of unfounded lawsuits, and increased unpredictability in the financial environment that fosters research in, and development of, new treatments for disease.

   We note that while all sponsors will have serious concerns if incorrect information is posted about their products, the consequences of the dissemination

of incorrect information may be particularly severe for small biotechnology companies with only one product, or only a small product portfolio.

4. The Draft Guidance does not provide a clear explanation of how and when sponsors will be notified when information is first posted to the site, and when changes are made to the information. Lines 216-218 state that FDA will notify the sponsor about inclusion of a product on the Drug Watch site "shortly before the first instance" of posting; BIO recommends that the Final Guidance be more specific as to the meaning of "shortly before." In our view two weeks would be the minimum appropriate advance notice, barring special emergency circumstances (circumstances which should be clearly delineated in any Final Guidance). Advance notice to the sponsor should include the source(s) of information on which FDA is relying to make decisions about posting information on Drug Watch, and copies of any special analyses of that information which have been performed by FDA. It should be possible for the sponsor to request postponement of the timing of posting information, based on appropriate reasons (such as evidence that the information being used to make a decision about a posting to Drug Watch is not scientifically or medically valid). Further, the Guidance should provide an explanation of how and when sponsors will be notified if changes are made to the information. The timing and accuracy of these notifications to the sponsor are critically important, to ensure that sponsors provide accurate information both to patients and health care professionals and to other government agencies, such as the SEC. We also suggest that FDA establish a mechanism for sponsors to seek Drug Safety Oversight Board (DSOB) review of posted information, and to provide for withdrawal or modifications to that information following such review.

If, despite the issues identified above, FDA proceeds to issue the Draft Guidance in final form, BIO requests that the Agency make additional revisions to address the many public health questions raised by the Draft. We have identified such revisions below, and in our Appendix 1 "Additional Specific Comments."

II. Policy Comments

A. Final Guidance Should Communicate Clearly That Site Information Is Incomplete

According to the Draft Guidance, the purpose of Drug Watch is to provide timely access to up-to-date and emerging information on drug risks, about which FDA has not made any regulatory decision. We note though that decisions made on the basis of incomplete information are not in the best interest of patients, and that Drug Watch would appear not to include discussion either of product benefits, or of risks already demonstrated and included in labeling. Therefore we believe that the site should contain a statement, prominently placed, that all therapeutic products have demonstrated benefits and risks, and that benefit information also may be emerging, none of which may be reflected fully

on the site. We suggest that the "Drug Specific Information" page provide a link to the approved labeling for every listed product. This would help provide patients and physicians the ability truly to do "one-stop shopping" for information about drugs. We also recommend that any Final Guidance clarify how FDA will harmonize, and how physicians and patients can manage, potentially confusing inconsistencies between the information on the site and that contained in the approved labeling.

B. Final Guidance Should Define Terms Clearly and Use Them Consistently

BIO believes that to be of most use, the site would have to have a clear and clearly articulated purpose. At lines 21-22, this purpose is described as "to identify drugs for which FDA is actively evaluating early safety signals." However the purpose of the site seems to be described differently at lines 36-37: "to provide a forum in which we can communicate emerging safety information to the public while we continue to evaluate that information." At lines 59-65, the information on the site is described variously as "drug risk information … as it emerges while the Agency is evaluating its significance," "the most up-to-date and emerging product information," "important emerging drug safety information," and "emerging safety information before we have fully determined its significance." Then, the Draft Guidance, in discussing what information will be posted, states (line 76) that the site will provide "information about drugs with significant emerging safety issues that FDA is evaluating."

BIO is concerned that these different and, in some ways, conflicting descriptions are confusing and could cause misinterpretation and misuse of the information on the site. We suggest that terms such as "signal" and "significant," terms of art in discussing product safety, be defined clearly and used consistently, both throughout this document and with other FDA documents related to product safety.

The word "associated" is also a term of art in discussing product safety. As we noted above, the "association" between an adverse event and a product is a critical component not only of medical decisions but also of products liability analysis. In its adverse event reporting regulations, FDA acknowledges this relationship through the use of a disclaimer (please see footnote 1, and Section IID of our comments). In FDA's Draft Guidance, there appears to be inconsistency in the use of the term, which could result in unintended consequences. For example, lines 96-97 mention "significant emerging risks that FDA believes may be associated with a drug, …" but then lines 100-101 provide an example of the type of information that could appear on the site, as "Drug B has been associated with serious … ." It is critically important to distinguish clearly FDA's view that an event **may be associated** with a product from its determination that an event **has been associated** with a product. Again, as these are technical terms of art, if this concept is not articulated precisely, the misunderstanding or misuse of the terms can cause both medical and legal consequences not intended by FDA.

C. Final Guidance Should Address Public Health Concerns

FDA needs to address the possibility that patients might overreact to information disseminated by FDA under the Draft Guidance. Not all patients will heed FDA's advice that patients seek professional advice before acting on the basis of Drug Watch information (*e.g.*, by discontinuing a medication or changing dosage), and these patients may suffer injury if they alter treatment when they should not have done so. We note that for patients who do heed the advice to consult a health professional, the Draft Guidance imposes costs on the healthcare system. If a prescriber visit is necessary, the associated costs – including additional diagnostic or other testing – should be driven by reliable information that has been documented and validated appropriately.

BIO is also concerned that patients could be confused about what it means, from FDA's perspective, for a product to be listed on the site. Lines 23-25 state that the drugs listed on the Drug Watch site are not "particularly risky or dangerous" and that FDA's listing is not "a statement . . . that the drug is dangerous or that it is inappropriate for use." Elsewhere, however, the Draft Guidance uses language suggesting that prescribers and patients should take a particular action in reaction to a listing. *See, e.g.*, Lines 153-154 ("Whether new and emerging safety information could significantly affect prescribing decisions. . ."), and Lines 162-163 ("whether an unapproved (off-label) use of the drug appears to pose a significant risk to patients"). We note that the question of whether to make a medical decision, and what that decision should be, cannot be answered from information that has not yet been evaluated by FDA. If Drug Watch is implemented, it will be critical for FDA to communicate very clearly the level of scientific rigor to which the information posted on Drug Watch has been subjected, and state very clearly whether prescribers and patients are being urged to take any particular action on the basis of that information. As we have stated above in the Introduction to this document, we believe that at a minimum, information posted to the Drug Watch site must be supported by substantiated evidence and comprehensible to patients and prescribers. We also urge that the site include disclaimer language similar to that in 21 C.F.R. 314.80(k),[1] modified as appropriate.

The Draft Guidance also does not sufficiently address removal of a drug or other changes to the Drug Watch site. According to the Draft, FDA will update the site regularly and may remove drugs from the page as safety issues are resolved or if there is no safety concern, but the Draft is not explicit about precisely how the changes on the site will be characterized and communicated. Comprehensive and timely communication about any changes is as important as communication about the initial safety concerns. The Draft Guidance provides specific language that will accompany a drug's first appearance on the site; it is important to include as well how FDA will characterize revised information, to ensure that patients clearly understand what has changed. This is particularly important

[1] "k) *Disclaimer.* A report or information submitted by an applicant under this section (and any release by FDA of that report or information) does not necessarily reflect a conclusion by the applicant or FDA that the report or information constitutes an admission that the drug caused or contributed to an adverse effect. An applicant need not admit, and may deny, that the report or information submitted under this section constitutes an admission that the drug caused or contributed to an adverse effect. …." (Such a disclaimer would, of course, need to be redrafted to be comprehensible to lay patients.)

if, upon further evaluation, the concern identified in a posting could not be substantiated. In such cases, information should be promptly removed from the web site and an explanation should be posted for patients and healthcare providers describing why the information was removed. In addition we recommend that, when a drug is removed from the site, FDA take steps to ensure that the reasons for this are communicated widely and quickly to prescribers and patients, *i.e.*, take steps beyond simply posting the information on Drug Watch (use "dear health care practitioner" letters, references on the FDA home page, press releases, and so on). The explanation for the removal of information from Drug Watch should reach all those who received the incorrect information.

D. Final Guidance Should Address Products Liability Consequences

Products liability is an issue of tremendous importance to BIO members. When private litigants advance unsubstantiated and unfounded tort claims against prescription drug manufacturers for personal injury, their actions, in the aggregate, can have substantial effects on the ability of the industry to innovate. Tort liability also affects the availability of therapeutic products to patients, and increases prices. We recommend that any Final Guidance discuss these product liability concerns, in a manner that helps to minimize unintended consequences.

FDA has recognized that products liability can have major public health consequences. In the preamble accompanying the 2003 proposal to amend FDA's safety reporting regulations, the Agency stated: "FDA is concerned that . . . liability misuse of these reports could imperil the credibility and functionality of this critical public health reporting system." 68 Fed. Reg. 12,406, 12,418 (Mar. 14, 2003). In 2000, FDA observed that "the use of labeling in product liability and medical malpractice lawsuits, together with increasing litigation costs, has caused manufacturers to become more cautious and include virtually all known adverse event information, regardless of its importance or its plausible relationship to the drug." 65 Fed. Reg. 81,082, 81,083 (Dec. 22, 2000). Indeed, FDA found approved labeling so unwieldy that the Agency has proposed comprehensive amendments to §§ 201.56 and 201.57.

Unverified safety signals already expose BIO members to substantial liability. Adverse event information reported to FDA under § 314.80 is only the first step in the Agency's process of managing postmarketing prescription drug risks. The mere fact that an adverse event has been reported does not mean that the risk profile of the drug has changed since approval. Indeed, FDA's own regulations make clear that this information requires additional verification and "does not necessarily reflect a conclusion by the applicant or FDA that the report or information constitutes an admission that the drug caused or contributed to an adverse effect." 21 C.F.R. § 314.80(k). Nevertheless, lawsuits are frequently initiated based on this information. That Drug Watch will also precipitate personal injury litigation is a virtual certainty.

FDA should not implement Drug Watch without a much more serious examination of Drug Watch's implications for products liability and, consequently, innovation, availability, and price. The Draft Guidance merely states (lines 24-25) that "listing of a

drug on Drug Watch should not be construed as a statement by FDA that the drug is dangerous or that it is inappropriate for use." At a minimum stronger language on the lack of correlation between FDA action and tort liability is needed (please see footnote 1 for an example of language that might be modified to serve as an appropriate disclaimer).

We also request that FDA reaffirm, in any Final Guidance, that its risk management decisions are frequently based on evidence that would not meet standards of proof applicable in common law tort actions. In 2002, the Agency promulgated regulations requiring risk information in the labeling of diphenhydramine-containing OTC drug products. 67 Fed. Reg. 72,555, 72,556 (Dec. 6, 2002). In response to comments questioning whether FDA had sufficient adverse event reports to justify the labeling requirement, FDA stated:

> Mandating a warning does not require a finding that any or all of the OTC drug products that contain diphenhydramine actually caused an adverse event, and FDA does not so find. . . . FDA's decision to act in an instance such as this one need not meet the standard of proof required to prevail in a private tort action (Glastetter v. Novartis Pharmaceuticals, Corp., 252 F. 3d 986, 991 (8th Cir. 2001)). To mandate a warning, or take similar regulatory action, FDA need not show, nor do we allege, actual causation.
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> The distinction between avoidance of risk through regulation and compensation for injuries after the fact is a fundamental one. In the former, risk assessments may lead to control of a toxic substance even though the probability of harm to any individual is small and the studies necessary to assess the risk are incomplete; society as a whole is willing to pay the price as a matter of policy. In the latter, a far higher probability (greater than 50%) is required since the law believes it is unfair to require an individual to pay for another's tragedy unless it is shown that it is more likely than not that he caused it * * *.
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> In re "Agent Orange" Product Liability Litigation, 597 F. Supp. 740, 781 (E.D.N.Y. 1984), aff'd., 818 F. 2d 145 (2d Cir. 1987) at 781. In making its decision, the agency follows "the preventive perspective that [ ] agencies adopt in order to reduce public exposure to harmful substances." Glastetter, 252 F.3d at 991, quoting Hollander v. Sandoz Pharmaceuticals, Corp., 95 F. Supp.2d 1230, 1234 n. 9 (W.D. Okla. 2000). This is what we have done here.

As this passage makes clear, it is not appropriate for private litigants to cite FDA regulatory action as evidence of a harm for which a sponsor may be found liable in tort. FDA should reaffirm this principle in connection with Drug Watch.

FDA should also, at the very least, make clear that sponsors *are not required* to disseminate Drug Watch information unless and until FDA has found it substantiated and it has been incorporated into the labeling. FDA has taken this position in the past. *See, e.g.,* The Pink Sheet, May 9, 2005, at 12 (the labeling is the legal standard against which the accuracy of sponsor statements are evaluated) (discussing remarks of CDER Acting Director).

III. Legal Issues

A. FDCA

The Draft Guidance is inconsistent with the statute's comprehensive system for the dissemination of information about prescription drug risks to the public.

Under this system, the sponsor or FDA identifies possible new risks through postmarket surveillance; information about these possible new risks is related by the sponsor to FDA or by FDA to the sponsor; and the sponsor and FDA evaluate this information to determine whether the possible risk is genuine. If FDA finds the risk substantiated, information about the risk is incorporated into labeling in cooperation with the sponsor. This information is then communicated to prescribers through labeling, and those prescribers relay the new risk information to patients in the context of an individualized discussion of risks *and* benefits.

In the Draft Guidance, FDA proposes to "communicate emerging safety information to the public while [the Agency] . . . continue[s] to evaluate that information." Thus, under the proposal, FDA would (1) give unsubstantiated risk information directly to patients, (2) without appropriate sponsor consultation, and (3) without the participation of qualified health care practitioners. The FDCA does not authorize FDA to do any of these things. Put another way, there is simply no room in the well-established risk analysis and communication system under the FDCA for the risk communication program envisioned by the Draft Guidance.

1. Lack of Substantiation

A feature of FDA's current system of prescription drug regulation is that the only risk information disseminated in labeling is information that has been analyzed by FDA and found to be substantiated. The Draft Guidance is inconsistent with the FDCA's comprehensive risk evaluation system because it expressly provides for the dissemination of "emerging" risk information that has not been substantiated. FDA should make clear in the Final Guidance that risk information will be disseminated through Drug Watch only if it meets the "substantiated evidence" standard. Adhering to this high standard

will ensure that FDA retains its proper role as a source of authoritative information about the risks and benefits of drugs.

The principal FDCA provision relating to the dissemination of risk information for drugs is Section 502(f)(1), 21 U.S.C. § 352(f)(1). Under that section, a drug shall be deemed to be misbranded unless its labeling contains "adequate directions for use." According to FDA regulations, this means "directions under which the layman can use a drug safely and for the purposes for which it is intended." 21 C.F.R. § 201.5. Because a prescription drug, by definition (21 U.S.C. § 353(b)), cannot be used safely by a layperson, FDA regulations provide an exemption from the "adequate directions for use" requirement. 21 C.F.R. § 201.100. A prescription drug qualifies for this exemption if its labeling complies with the format and content requirements of 21 C.F.R. §§ 201.56 & 201.57.

These regulations act as a template for an important part of the new drug application (NDA). The NDA must include, among other information, draft labeling that complies with §§ 201.56 & 201.57. It must also include comprehensive safety data (21 C.F.R. § 314.50(d)(5)(vi)) to substantiate the risk information included in the sponsor's proposed labeling. FDA scrutinizes the risk information in the proposed labeling based on the data and information in the NDA. The Agency may submit risk-related questions to an expert advisory committee before reaching a final decision. 21 C.F.R. § 14.171. When FDA approves a drug, it also approves the labeling, including the risk information. 21 C.F.R. § 201.57(d)-(g).

In the four risk-related sections required in approved labeling, information cannot appear unless FDA has found it adequately substantiated. Under § 201.57(d), the "contraindications" section cannot address "theoretical possibilities." Thus, for example, "if hypersensitivity to the drug has not been demonstrated, it should not be listed as a contraindication." Similarly, § 201.57(e) makes clear that the warnings section may include only those "serious hazard[s]" for which there is "reasonable evidence of an association . . . with a drug." Drug interaction information may be included in the precautions section only if it is relevant to clinical use of the drug in patients. This means, for example, that animal and in vitro data may be included only "if shown to be clinically relevant." 21 C.F.R. § 201.57(f)(4)(i). Under § 201.57(g), adverse events may be included in labeling only if they are "reasonably associated with the use of the drug."

As these provisions make clear, the labeling is not designed to summarize all that is known about the drug, such as information about "emerging," but as-yet unsubstantiated, risks. Rather, the labeling summarizes the information that FDA has determined, based on a thorough review of the NDA, is necessary for the product to be used safely and effectively. *See, e.g.*, 65 Fed. Reg. 81,082, 81,082-83 (Dec. 22, 2003) (labeling contains only information "essential" for prescribing decisions); 44 Fed. Reg. 37,434, 37,435, 37,441 (June 26, 1979) (labeling contains only statements determined by FDA to be necessary to prescribe safely and effectively and substantiated to FDA's satisfaction). The labeling, by design, contains only substantiated, clinically relevant information about the benefits and, of importance here, the risks of the drug.

After approval, the rule is the same: risk information must be substantiated before it can be added to labeling. The FDCA and FDA regulations prescribe several procedures to assure that FDA receives information about risks that become apparent after a drug is approved. Under FDCA § 505(k) and FDA regulations, a manufacturer must submit prompt reports of serious, unexpected drug experiences as well as periodic reports of all information relating to the safety of the drug. 21 C.F.R. §§ 314.80, 314.81. FDA reviews this information and directs manufacturers to amend the risk-related sections of labeling only if a new risk is deemed to be genuine. As in the pre-approval period, expert advisory committees play an important role after approval in determining whether labeling should be revised.

There are sound public health reasons for FDA to ensure that the Agency disseminates only substantiated risk information. Warnings about speculative risks threaten prescribers' ability to identify clinically meaningful hazards, for example. *Carlin v. Superior Court*, 920 P.2d 1347, 1353 (Cal. 1996) ("[E]xperience suggest[s] that if every report of a possible risk, no matter how speculative, conjectural, or tentative, imposed an affirmative duty to give some warning, a manufacturer would be required to inundate prescribers indiscriminately with notice of any and every hint of danger, thereby inevitably diluting the force of any specific warning given."), *quoted with approval in Dowhal v. SmithKline Beecham Consumer Healthcare*, 32 Cal. 4th 910, 931 (Cal. 2004).

FDA prohibits manufacturers from disseminating any information about a drug that is not sufficiently substantiated. Promotional claims about a drug's safety may not be false or misleading, and efficacy claims in promotion must be supported by "substantial evidence," which (in FDA's view) means two adequate and well-controlled clinical trials. 21 U.S.C. §§ 352(a) & (n), 355(d); 21 C.F.R. §§ 202.1(e)(4) & (5)(i), 314.126. On this basis, FDA does not allow the dissemination of effectiveness information derived from, for example, single open-label clinical investigations. *See, e.g.*, Letter from Michelle Safarik, MSPAS, PA-C & Jialynn Wang, Pharm.D., LT, USPHS, Regulatory Review Officers, Division of Drug Marketing, Advertising, and Communications to Elizabeth M. Zola, Pharm.D., Associate Director, Regulatory Affairs, Ross Products Division, Abbott Laboratories (July 15, 2005). As noted above, a manufacturer can add risk information to labeling only if that information is sufficiently substantiated. As we also noted earlier in these comments, FDA explained in its seminal report, Managing the Risks From Medical Product Use (May 1999) (Part 1), that "FDA's role in reducing risk involves ensuring that accurate, substantiated, and balanced information about a product is available to the prescriber and the patient."

FDA should not hold regulated entities to the regulatory standard for drug information but not hold itself to anything resembling that standard. *Giford Pinchot Task Force v. United States Fish & Wildlife Serv*., 378 F.3d 1059, 1072 (9th Cir. 2004) ("It would create a double standard to give the agency a free pass when private litigants are routinely constrained to show error by focusing on the record created by the agency . . . .") (citing *Morgan v. United States*, 304 U.S. 1 (1938)); *Goins v. Heckler*, 1985 U.S. Dist. LEXIS 14563 (N.D. Ill. 1985) (administrative law judge may not "[create] a double standard

whereby evaluations arranged by the claimant are disbelieved while those arranged by the agency are considered). Yet that is exactly what FDA is proposing here.

FDA should make clear that risk information will be disseminated through the Drug Watch only if it meets a high standard of substantiation. BIO believes that it would be appropriate for FDA to post information on the Drug Watch site about an approved product if the agency has determined that an "emerging" risk must be addressed in the FDA-approved labeling for the product and has completed discussions with the sponsor under 21 U.S.C. 355(e) to amend that labeling to include information on that risk. If FDA were to adopt that standard for the Drug Watch, then the agency could also provide through the Drug Watch site hyperlinks to the updated revised labeling. The site would then provide, in a single, convenient location, the newest substantiated risk information about prescription drugs.

Alternatively, BIO believes it would be appropriate for FDA to post information on the Drug Watch site only after the agency has determined that an "emerging" risk is of sufficient importance that it warrants further action on the agency's part such as referral to an advisory committee for analysis. FDA regulations give high priority to advisory committee review of marketed drugs that "pose newly discovered safety hazards." 21 C.F.R. 14.171(b)(2). This regulation does not contemplate that advisory committee review will be used with respect to any potential risk identified after approval, no matter how minor. Rather, it contemplates use of advisory committees when a risk has been sufficiently characterized and FDA can conclude that is presents a bona fide "safety hazard." By linking listing on the Drug Watch site to referral of an issue to an advisory committee, FDA could, BIO believes, ensure that the site is not used to disseminate inaccurate or unsubstantiated safety information to patients, contrary to the FDCA.

2. Role of Sponsor

The Draft Guidance is inconsistent with FDA's best practices because it expressly provides for the dissemination of risk information without appropriate sponsor consultation.

The sponsor is the expert on the risk profile of its own drug. Sponsors are responsible for conducting clinical investigations of new drugs, and must ensure that these investigations are properly monitored. 21 C.F.R. §§ 312.50, 312.56(a); *see also* 21 C.F.R. §§ 312.53(d), 312.50; 312.56(d), 56.111(a)(6); 45 C.F.R. § 46.111. The summary of safety information included in the NDA, which gives FDA reviewers their introduction to the risk profile of a new drug, is prepared by the sponsor. 21 C.F.R. § 314.50(d)(5)(vi). Sponsors are also responsible for processing postmarketing risk information in the first instance. 21 C.F.R. § 314.80(b). Sponsors, not FDA, are charged by the FDCA with conveying FDA-approved risk information to prescribers (and, through them, patients) in the form of the FDA-approved labeling. 21 U.S.C. § 352(f)(1); 21 C.F.R. § 201.100.

Instead of leveraging this expertise to ensure that risk information in labeling is of this highest possible quality, FDA appears to be proposing an "end run" around labeling

negotiations with sponsors. As the statute makes clear, Congress has considered specifically how postmarketing risk information should be added to labeling and has required FDA to work with the sponsor. Because the Draft Guidance proposes to allow FDA to convey risk information directly to patients and prescribers without waiting for the labeling negotiations to conclude and revisions to be finalized, it is inconsistent with the FDCA.[2]

3. Role of Prescriber

The Draft Guidance is also inconsistent with the role of the prescriber under FDCA. For prescription drugs, the FDCA and FDA regulations contemplate that patients will receive risk information in the context of an individualized discussion of risks and benefits with a prescriber. As noted, and as FDA regulations recognize, it is impossible for a sponsor to write "adequate directions for use" of a prescription drug by a lay person. These directions, in the form of the FDA-approved labeling, are provided to the practitioner, who in turn discloses risk information to the patient as appropriate.

The role of the practitioner in FDA's risk management system is central. As FDA observed in a 1998 *Federal Register* final rule preamble, "Health care professionals bear the primary responsibility for informing individuals about patient-specific benefits, risks, and directions for using prescription medication." 63 Fed. Reg. 66,378, 66,384 (Dec. 1, 1998).[3] FDA also explained in Managing the Risks from Medical Product Use (May 1999) (Part 1): [A]fter FDA evaluates the risks and benefits for the population, the prescriber is central to managing risks and benefits for the individual."

In the existing system erected by the FDCA and FDA regulations, the practitioner serves as a learned intermediary, digesting the authoritative information in FDA-approved labeling supplied by the manufacturer and translating it into an individualized assessment of risk, in the context of clinical benefit, for the patient. Therefore BIO believes that Drug Watch, which provides for the dissemination of unsubstantiated risk information directly to patients, is thus in tension, at least, with the language and the entire structure of the FDCA.

The inconsistency of the Draft Guidance with the FDCA is confirmed by § 705(b), 21 U.S.C. § 375. That provision authorizes FDA to "cause to be disseminated information regarding . . . drugs . . . in situations involving . . . imminent danger to health, or gross deception of the consumer." Yet the Draft Guidance applies only to "emerging" risk information that has not been substantiated. This information is too uncertain to qualify

[2] Moreover, to the extent that the information posted on the Drug Watch could have such dire commercial consequences as to be tantamount to withdrawal of a product from the market, taking such an action without notifying the sponsor first raises Due Process and fundamental fairness concerns.

[3] The courts, too, have recognized that risk information for prescription drugs is conveyed to patients only through prescribers. *See, e.g., Felix v. Hoffmann-LaRoche, Inc.*, 540 So.2d 102 (Fla. 1989) ("[T]he manufacturer's duty to warn . . . was directed to the prescriber rather than the patient . . . because the prescribing prescriber, acting as a 'learned intermediary' between the manufacturer and the consumer, weighs the potential benefits against the dangers in deciding whether to recommend the drug to meet the patient's needs.").

as information related to an imminent danger within the meaning of this provision. Moreover, there is no indication from the Draft Guidance that FDA believes "emerging" risk information relates to "gross deception." In carefully circumscribing FDA's publicity authority, § 705 confirms what is apparent from the entire FDCA – that FDA cannot disseminate unsubstantiated risk information directly to the public.

B. APA Rulemaking Requirements

The Draft Guidance constitutes a change in regulatory regime and should be established only if FDA were to follow the notice-and-comment rulemaking procedures of the Administrative Procedure Act (APA), which it has not done here.

As discussed above, the Draft Guidance constitutes a fundamental change in FDA's existing system for addressing emerging risk information. Instead of ensuring that risk information is substantiated before disseminating it in the labeling to prescribers, FDA is proposing to provide unsubstantiated, "emerging" risk information directly to patients. Indeed, FDA concedes that, under the existing regime, it provides risk information only "when we [are] . . . certain of its significance or it prompt[s] . . . a regulatory action." Under the Draft Guidance, now FDA says it will "make important drug safety information available to health care professionals and patients" through Drug Watch. 70 Fed. Reg. at 24,606. FDA is also proposing to preempt the labeling negotiations required under FDCA § 505(e). This goes too far – certainly in the absence of any rulemaking. FDA should not fundamentally alter an existing regulatory regime to this extent without engaging in rulemaking under the APA. *See United States Telecom Ass'n v. FCC*, 400 F.3d 29, 35 (D.C. Cir. 2005) ("[F]idelity to the rulemaking requirements of the APA bars courts from permitting agencies to avoid those requirements by calling a substantive regulatory change an interpretative rule.") (citations omitted); *Alaska Prof. Hunters Ass'n, Inc. v. FAA*, 177 F.3d 1030, 1034 (D.C. Cir. 1999).

Even if the Draft Guidance does not fundamentally alter the existing regulatory regime, FDA must follow the APA rulemaking requirements. It is a well-established rule of administrative law that a federal agency can create a binding norm having legal consequences for private parties (or for the agency itself) only after going through notice-and-comment rulemaking. *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). Drug Watch binds FDA in certain respects and has serious legal consequences for BIO members and other regulated entities. As discussed above in Section IID of these comments, the products liability implications of FDA's proposal are potentially enormous. Accordingly, FDA may not lawfully adopt Drug Watch by publishing a guidance document.

C. Information Quality Problems

The Draft Guidance raises issues under several other federal statutory and regulatory policies governing the quality of information disseminated by federal agencies, including FDA. In the Information Quality Act, Congress directed the Office of Management and Budget (OMB) to issue guidelines to "provide policy and procedural guidance to Federal agencies for ensuring and maximizing the quality, objectivity, utility and integrity of information" they disseminate. Pub. L. No. 106-554, § 515(a). The Paperwork Reduction Act, 44 U.S.C. § 3501 *et seq*., requires OMB to "develop and oversee the implementation of policies, principles, standards, and guidelines to . . . apply to Federal agency dissemination of public information." Executive Order 12866, 58 Fed. Reg. 51,735 (Oct. 4, 1993), directs OMB to provide guidance to federal agencies on regulatory planning and provides that "[e]ach agency shall base its decisions on the best reasonably obtainable scientific, technical, economic, or other information." E.O. 12866, §§ 1(b)(7) & 2(b). As discussed below, it appears from the Draft Guidance that FDA will be disseminating risk information about prescription drugs without complying with, at minimum, the Information Quality Act or with OMB's Peer Review Bulletin, which was issued on the authority of that statute.

1. Information Quality Act

The Information Quality Act (IQA) requires federal agencies to use and disseminate accurate information. The statute required the Director of OMB by September 30, 2001, to issue guidelines

> that provide policy and procedural guidance to Federal agencies for ensuring and maximizing the quality, objectivity, utility, and integrity of information (including statistical information) disseminated by Federal agencies . . . .

Under the statute, the OMB guidelines must require each federal agency to which the guidelines apply, in turn, to issue guidelines ensuring and maximizing the quality, objectivity, utility, and integrity of its information, no later than a year after the date of issuance of the OMB guidelines. On February 22, 2002, OMB published the final version of the guidelines required by the IQA. *See* Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by Federal Agencies, 67 Fed. Reg. 8,452 (2002). According to the OMB guidelines, each federal agency to which the IQA applies must adopt a basic standard of quality of information as a performance goal, and must also adopt specific standards of quality appropriate for the various categories of information they disseminate. *Id*. at 8,459. As required by the IQA, the OMB guidelines provide, further, that each federal agency must publish its own data quality guidelines. *Id*. FDA's data quality guidelines appear in the Department of Health and Human Services (DHHS) "Guidelines for Ensuring the Quality of Information Disseminated to the Public." *See* http://www.hhs.gov/infoquality/fda.html.

The FDA Guidelines indicate that the Agency has "established a number of quality assurance policies, standards, and processes for ensuring the quality of the information we disseminate to the public. . . . FDA reviews the quality (including the objectivity, utility, and integrity) of information before it is disseminated and treats information quality as integral to every step of the development of information, including its creation, collection, maintenance, and dissemination." In those Guidelines, FDA states: "We only disseminate information that we believe will be useful to the public or a segment of the public."

Contrary to this representation, FDA states in the Draft Guidance that it will disseminate drug risk information before the Agency has determined that it has any clinical significance. Lines 23-25 state that the drugs listed on the Drug Watch site are not "particularly risky or dangerous" and that FDA's listing is not "a statement . . . that the drug is dangerous or that it is inappropriate for use."[4] This language suggests that prescribers and patients should not take any particular action in response to the emerging risk information provided through Drug Watch. It suggests that the appropriate course is to wait for FDA to reach a final determination on whether the suspected risk is genuine and what, if any, regulatory action (e.g., relabeling) is necessary to address the new risk. Because FDA contemplates that neither prescribers nor patients will take any specific action in response to the information disseminated through Drug Watch, the information does not appear to meet the "utility" requirement and conflicts with FDA's own information quality guidelines and with the Information Quality Act.

The Draft Guidance repeatedly makes clear that the information to be disseminated through Drug Watch is information of highly uncertain significance. "The Drug Watch," FDA states, "is intended to identify drugs for which FDA is actively evaluating early safety signals." FDA also indicates that identification of a drug on Drug Watch would signify that the Agency "is attempting to assess the meaning and potential consequences of emerging safety information." FDA thus concedes that the information it intends to provide under the Draft Guidance has not yet been assessed in any meaningful way, or in any way that would provide prescribers and patients with advice on the extent to which, if at all, they should modify use of the drug.

FDA also concedes in the Draft Guidance that the information to be provided through Drug Watch will be disseminated during the "period of uncertainty" that exists while FDA and the sponsor are evaluating the information. The purpose of this evaluation, indicates the Agency, is "to determine whether there is a real safety concern related to the drug and whether regulatory or other action is appropriate." And again: "The purpose of the Drug Watch Web page is to provide a forum in which we can communicate emerging safety information to the public while we continue to evaluate that information." As this language makes clear, the information FDA would supply to the public via Drug Watch

[4] In other places, the Draft Guidance suggests that prescribers and patients should respond to the Drug Watch by acting. *See, e.g.,* Lines 153-154 ("Whether new and emerging safety information could significantly affect prescribing decisions . . ."); Lines 162-163 ("whether an unapproved (off-label) use of the drug appears to pose a significant risk to patients").

would not yet have been evaluated in any meaningful way and thus would be unsubstantiated and of unknown importance.

Yet it is equally clear that prescribers and patients will take action based on the information provided through Drug Watch, no matter how much the Agency tries to disclaim its importance. FDA is the federal agency charged by Congress with ensuring the safety, effectiveness, and proper labeling of prescription drugs. 21 U.S.C. §§ 352(a) & (f)(1), 355, 393. As discussed above, its pronouncements on issues relating to drug risks are authoritative. BIO believes it is extremely likely that many patients will simply discontinue use of a drug identified through Drug Watch, despite FDA's statements on the site encouraging patients to consult a prescriber before doing so.

To comply with IQA, FDA must ensure that all risk information it distributes to the public has been sufficiently substantiated. As currently conceived, Drug Watch does not meet that standard.

2. OMB Peer Review Bulletin

The Draft Guidance also raises issues under peer review requirements applicable to federal agencies. OMB's Final Information Quality Bulletin for Peer Review on December 15, 2004, establishes the following general rule: "To the extent permitted by law, each agency shall conduct a peer review on all influential scientific information that the agency intends to disseminate." OMB, Final Information Quality Bulletin for Peer Review § II(1) (Dec. 15, 2004). Under the Bulletin, "influential scientific information" includes "data, . . . analyses, technical information, or scientific assessments based on . . . public health and medical sciences" that "the agency reasonably can determine will have or does have a clear and substantial impact on important public policies or private sector decisions." *Id.* § I(5) & (6).[5] "Highly influential scientific information" – that is, influential scientific information that the agency determines to be a scientific assessment that could have a potential impact of more than $500 million in any year, or that is novel, controversial, or precedent-setting or has significant interagency interest – is subject to heightened peer review requirements. *Id.* § III.

The risk information covered by the Draft Guidance is subject to the Bulletin's general peer review requirement. According to the Draft, FDA will use a new page on the Agency's web site, to be known as "Drug Watch," to "provide information about drugs with significant emerging safety issues that FDA is evaluating." The page will include: (1) "factual information about newly observed, serious adverse events associated with the use of a drug that have been reported to FDA"; (2) "information about significant emerging risks that FDA believes may be associated with a drug, but that might be avoided by appropriate patient selection, monitoring, or use of concomitant therapy"; or (3) information about a new risk minimization procedure a sponsor has implemented to

[5] The general peer review requirement also applies to "any communication or representation of knowledge such as facts or data, in any medium or form, including textual, numerical, graphic, cartographic, narrative, or audiovisual forms." The definition of "scientific information" in the Bulletin also encompasses "information that an agency disseminates from a web page." *Id.* § I(5).

"alert patients and healthcare professionals to important changes in how a drug should be prescribed, dispensed, or used." FDA will also use Drug Watch to provide information about the status of Agency analysis of emerging safety issues. This information constitutes technical information based on public health and medical sciences. Given that FDA's stated objective for Drug Watch is to "make emerging safety information available to the public so that healthcare professionals and patients can consider the information when making decisions about a patient's medical treatment," it is hard to see how this information would not "have a clear and substantial impact on important public policies or private sector decisions."

There is no evidence that information posted on FDA's web site under the Draft Guidance will have complied with the Bulletin's peer review requirement. FDA will, according to the Draft, rely on the DSOB to decide which products will be included on Drug Watch. The Draft Guidance also states that the DSOB "may engage as consultants the Chairs of FDA Advisory Committees and other external scientific experts, as well as consumer and patient representatives to present their views regarding emerging drug safety issues." This does not comply with the Bulletin's requirements that an agency instruct peer reviewers to prepare a report describing the nature of their reviews and their findings and conclusions. *Id*. § II(5). Nor does the Draft Guidance provide that final peer review reports will be disseminated on FDA's web site along with all materials related to the peer review (including any charge statement, the peer review report, and any Agency response).

FDA cannot properly claim that the Draft Guidance is covered by an exemption from the Bulletin's general peer review requirement. The only two conceivably applicable exemptions in Section IX of the Bulletin are subsections 2 and 3. Section IX(2) does not apply to the information to be posted on the Drug Watch page because there will be no "individual agency adjudication or permit proceeding." The FDCA provides for FDA to use an "individual agency adjudication or permit proceeding" to address risk information that first emerges about an approved drug during marketing. That provision is Section 505(e) of the FDCA. FDA could choose to invoke this procedure. But to do so would require the agency to give the sponsor an opportunity for a hearing (if FDA determined the new risk was serious enough to warrant revocation of the NDA) or, at a minimum, would require the agency to discuss labeling changes with the sponsor. These procedural safeguards reflect Congress' determination that FDA should engage directly with sponsors in incorporating newly discovered risk information into an existing approval. They also are consistent with the general notion in the Bulletin that an "individual agency adjudication or permit proceeding" entails dialogue between the adjudicating or licensing government agency and a particular party. Here, however, FDA proposes to act on emerging risk information without directly engaging the sponsor outside the context of an individual adjudication or proceeding on the approval. Under the circumstances, it is hard to see how what FDA is proposing to do fits within the Section IX(2) exception.[6]

[6] The product approval process is also distinguished from postmarketing surveillance in the information quality guidelines applicable to FDA, lending further support to BIO's contention that this exemption does not apply. *See* http://www.hhs.gov/infoquality/fda.html.

Moreover, Section IX(3) of the Bulletin does not apply because the information to be disseminated will not be "time sensitive." As FDA states in the Draft Guidance, information will be posted before the Agency has determined whether it is clinically significant and should be acted on by prescribers and patients. Under these circumstances, it is hard to see how this information can be fairly described as "time sensitive. Until FDA has made a determination that the information is in fact actionable from a regulatory perspective, it cannot assert that there is urgency in providing information to patients or providers. Again, contrast this with the requirements of § 705(b), 21 U.S.C. § 375, authorizing agency action "in situations involving … imminent danger to health …." But the Draft Guidance makes abundantly clear that this information is being posted during the "period of uncertainty" where no imminent hazard has, in fact, been established.

Like the IQA, the OMB Bulletin is designed to ensure that federal agencies only provide information that is accurate and useful to the public. The peer review mechanism is one of the tools OMB has selected to achieve this objective. FDA must use that mechanism as provided by the Bulletin, particularly here, where it is virtually certain that prescribers and patients will take action based on the information the Agency supplies. In short, FDA cannot implement Drug Watch without first ensuring that there are adequate mechanisms in place to comply with the Bulletin's peer review requirement.[7]

IV. Conclusion

While BIO supports the goal of the Draft Guidance to provide information to patients and prescribers – information that will assist in making appropriate and informed treatment decisions – we do not believe that FDA will be able to accomplish this goal through the Drug Watch program as described in the Draft Guidance. We believe that if FDA moves forward with the Drug Watch program as described, the unwanted consequences could well adversely impact public health.

The FDCA establishes a particular system for the dissemination of risk information in which FDA, sponsor, and prescriber each play a special role. However because the Draft Guidance proposes fundamental changes to this statutorily prescribed system, it is inconsistent with the FDCA. At a minimum, serious APA issues would arise if FDA alters the existing system to the extent provided by the Draft Guidance without engaging in notice-and-comment rulemaking.

FDA should seriously examine the implications of Drug Watch for products liability and, consequently, innovation, availability, and price. Whether or not FDA engages in such examination, the Agency should include in any Final Guidance stronger language on the lack of correlation between FDA action and tort liability.

[7] Without peer review in accordance with the OMB Bulletin, it is also highly questionable whether the information disseminated via the Drug Watch will meet the "objectivity" requirement of FDA's data quality guidelines.

We appreciate the opportunity to comment on the Draft Guidance. If there are questions about these comments, please do not hesitate to contact us.

Sincerely,

/s/	/s/
W. Charles Lucas Vice President and General Counsel	Sara Radcliffe Managing Director, Scientific and Regulatory Affairs

cc: Paul Noe, Office of Management and Budget
Mark Kesselman, Office of Management and Budget

Appendix 1

ADDITIONAL SPECIFIC COMMENTS

Lines 19-20 indicate that site information is intended for both patients and health care professionals. BIO believes that the usefulness of the information may be increased by separately identifying information primarily intended for prescribers and that primarily directed to patients.

Lines 29-40 lay out the crucially important concepts that all products have risks, that benefits and risks must be considered together in making decisions about therapy and treatment options, and that more information about risks may emerge after a product has been on the market for a time. This material should be provided on the Drug Watch site, as opening information that precedes the new risk data. Further, it should be stated clearly that inclusion of a product on the Drug Watch site is neither a statement that the product is dangerous nor a recommendation from FDA to stop taking it, or stop prescribing it.

Lines 92-93 state that "Posting this information . . . will alert patients and healthcare professionals to potential safety risks while FDA is still evaluating . . ." We suggest that this sentence include a reference to the fact that the product sponsor also is evaluating the strength of the relationship between the drug product and the adverse event, by stating ". . . while FDA and the sponsor are still evaluating . . ."

Additionally, merely "posting this information…" to the website does not necessarily communicate a message unless users actively solicit the information by accessing Drug Watch. There is no guarantee that providers and patients will routinely access this site. Therefore, BIO recommends that FDA actively communicate Drug Watch postings and updates to a wider audience in a consistent manner i.e., via e-mails, press releases, and news conferences.

Lines 112-114 refer to information available under the Freedom of Information Act (FOIA), stating that "*Most* of the information … on the Web site … is now made available to the public … in response to … FOIA requests" (emphasis added.) We recommend that the Final Guidance clarify whether, in fact, the Agency intends to include on the site information that is not now currently available publicly.

Lines 120-124 spell out the disclaimer indicating that FDA has done only a "preliminary analysis" of the data. However, there appears to be no discussion in the Draft Guidance regarding the nature of this preliminary analysis. BIO urges that the Final Guidance provide more detail about who will be conducting this analysis, how the analysis will be conducted, and who will be involved in the final decision about what to include on the site. (For example, will outside advisors be involved and, if so, will this be in the form of an entire advisory committee or just selected members of a committee? What factors will play into that determination? Will all analyses be reviewed by the Center Director before

information is included on the Web site or will some decisions about what to include on the site be made a lower levels within the Center? If so, which kinds of decisions, which kinds of products, or which kinds of risks? How extensive will the preliminary analysis be? Will literature review be involved? When and to what extent will there be contact with the sponsor to obtain additional information or verification? Will any primary data be reviewed? What are the standards against which the information will be evaluated?)

We recommend that FDA include a statement that the posted information may be subject to more thorough analyses and verification (as we state in the Introduction to this document, we believe that information posted on Drug Watch should be at a minimum supported by substantiated evidence and comprehensible to patients and prescribers).

Lines 134-136 indicate that the site will include information on ". . . risks associated with off-label uses." It is not clear in the Draft Guidance what process FDA will use to determine when to list risk information about off-label uses, how the site will identify which uses of a product are labeled and which are not, and how it will be made clear why the product risks relate only to a specific off-label use and not to any other use of the product. This latter is especially important, to ensure that patients receiving the product for a labeled purpose do not mistakenly discontinue use of the product.

Footnote 5 (page 4) includes important information that should be presented in the body of the Guidance, along with an explanation of the processes for developing Patient Information and Health Care Professional Information Sheets, including how DSOB staff will work with others at FDA, and with sponsors, to obtain the necessary data; what will trigger revisions to the Sheets; and how patients and health care professionals will be notified of revisions. The existing footnote also provides the wording of the disclaimer regarding information on the Drug Watch site, stating that FDA has not reached a conclusion and plans to update information as needed. BIO urges that the disclaimer also include the following: "This information is accurate as of [date]. The most current version of the information can be obtained at [URL, telephone number, address]."

Lines 222-246 caution against use of the information on the Drug Watch site as promotional, such as for the purpose of comparative claims, and cite legal prohibitions against using material in claims that is not supported by "substantial evidence or substantial clinical experience." The Draft then states "Neither the fact that a drug appears on the Drug Watch nor the specific information posted about that drug will generally constitute (either separately or collectively) substantial evidence or substantial clinical experience to support a comparative safety or effectiveness claim." BIO believes that when it posts information, FDA should indicate clearly whether information on the site does or does not constitute "substantial evidence" or "substantial clinical experience" to support a comparative safety or effectiveness claim.

As we have stated elsewhere in our comments, we believe that at a minimum, information posted to the site must be determined by FDA to be supported by substantiated evidence and comprehensible to patients and prescribers. The threshold that we have suggested appears to be inconsistent with FDA's statements throughout the

Draft, that FDA will post information to the site which is preliminary, in need of further and evaluation, and not a sufficient basis for a regulatory decision. We have noted elsewhere that clarity about the validity and implications of the information on the site is important for patients and health care prescribers; here we note that clarity on this point is also important for others such as the media, tort attorneys, investors, financial advisors, and others, who may attempt to use the site information (or the mere fact of a product's listing on the site) for purposes totally different from making appropriate medical decisions. Unless everyone in the public likely to review the information on the Drug Watch site clearly understands the nature of this information, we believe there will be unintended and potentially detrimental consequences, such as prescribers unnecessarily practicing defensive medicine; formulary committees rejecting essential products or removing them from formularies on inconclusive and unsubstantiated evidence; and frivolous and costly lawsuits. We urge the Agency to take into account that it is possible members of the public will access the site and attempt to use the information for their own purposes – purposes that will not necessarily relate to FDA's purpose in establishing Drug Watch.