September 11, 2007

BIO White Paper on
RETROACTIVE APPLICATION OF FDA GUIDANCE

In 2006, the Food and Drug Administration (FDA) released a draft guidance document on patient-reported outcome measures. *See* "Draft Guidance for Industry, Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims" (hereafter "Draft PRO Guidance"). The Draft PRO Guidance was published in order to articulate standards under which companies will conduct *future* studies of patient-oriented outcomes of FDA-regulated products (also commonly called "quality of life" studies). However, BIO has recently become aware that FDA has requested that at least one biologics manufacturer reassess, based on the PRO Draft Guidance, quality of life statements included for many years in approved product labeling.[1]

This white paper sets forth BIO's general views on several critical points: 1) FDA should not seek to remove accurate information from approved labeling based on the existence of a guidance; 2) there are strong legal and policy arguments against retroactive application of rules, all of which are even stronger when applied to *draft* guidance documents that do not reflect agency policy; and 3) patients' access to information should not be restricted based on draft guidance – in fact broader use and access to such information should be encouraged.

BACKGROUND

FDA has included quality of life claims in drug labeling for many years. The studies that supported the claims were conducted many years ago and the scientific methods and instruments have, of course, changed over time. If FDA were to now apply the 2006 standards for those scientific methods and instruments to drugs previously approved, FDA would be taking a

[1] The FDA has published a postmarketing commitment "[t]o examine the "quality of life" (QOL) claims in the Clinical Experience section of the Epogen product labeling and to…perform an assessment of the patient-reported outcome (PRO) data used to support the PRO claims. This analysis of the PRO data will determine the extent to which the PRO data met the criteria described in the FDA guidance document entitled, "Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims"…" (available at http://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm?StartRow=7&StepSize=1&Paging=Yes).

surprising position – that it is permissible and even desirable to retroactively apply draft product approval guidance to drug products approved many years ago.

This would be bound to create havoc, because it would inexorably lead to a situation where companies must constantly re-review non-safety-related data under ever-changing standards. Retroactive application of the Draft PRO Guidance could apply to dozens of drugs, given that approximately 30 percent of all drugs approved between 1997 and 2002 contain patient-reported outcomes (PRO) data in the labeling.[2] If the agency were to broadly apply the standards in the Draft PRO Guidance to these products, dozens of companies would face an unsettled regulatory landscape in which study data is constantly being reassessed under evolving standards.

As discussed below, there are many well-founded arguments against the retrospective application of new government standards. Indeed, the Supreme Court has stated "[r]etroactivity is not favored in the law," and "administrative rules will not be construed to have retroactive effect unless their language requires this result." *Bowen v. Georgetown Univ. Hosp.*, 488 U.S. 203, 208 (1988). This basic legal tenet is even more compelling when FDA applies a draft guidance (not a rule) to an approved (as compared to a pending) application. *See, e.g.*, FDA Docket No. 1999P-2725/PDN1 (Aug. 7, 2000) ("Were FDA to use [a statutory provision] to reopen, for example, PMA approvals the agency issued before [the statute's] effective date, the agency would be using new authority to undo transactions completed in the past.").

FDA has long encouraged companies to provide drug information directly to patients through patient package inserts and other patient-directed brochures. FDA has also encouraged companies to study patient-reported outcomes so that patients can have access to meaningful information about both the benefits and risks of treatment and about potential treatment outcomes conveyed in language that patients understand. The agency's goal of comprehensive and balanced communication to patients about the benefits and risks is one of the factors that led to the development of the Draft PRO Guidance.

But the retroactive application of labeling standards risks creating just the opposite effect – data gathered from patients many years ago under standards relevant at the time would be at risk of being removed from drug labeling because those data might not meet changing standards, even where there is no public health or safety reason to do so. As a result, the agency could ask companies to *remove* patient-directed statements from labeling – statements included in the labeling in the first instance because of the agency's efforts to promote patient labeling.

Retroactive application of labeling standards would contradict several bedrock FDA policies and could have broad and lasting implications for both patients and industry.

KEY POLICY CONSIDERATIONS

FDA Has a Long-Standing Policy Against Retroactive Application of Approval Standards

[2] *The Importance of Patient-Reported Outcomes . . . It's All About the Patients*, FDA CONSUMER REPORT (Nov.-Dec. 2006) (available at http://www.fda.gov/ fdac/606_toc.html).

If FDA were to apply new approval standards to previously approved products, it would put into place a never-ending review process that requires constant re-evaluation of data under changing standards. As a result, FDA has long applied a presumption *against* the retroactive application of FDA policies, particularly with respect to product approval criteria such as those articulated in the Draft PRO Guidance. FDA has made this very clear through formal agency position papers.

CDER's *Manual of Policies and Procedures* specifically instructs staff that "[r]etroactive application of a new policy should be avoided unless there is a public health and safety reason for making the policy effective retroactively."[3] It is difficult to discern a health or safety reason mandating the application of standards for quality of life labeling. These statements discuss how patients in clinical trials reported certain measures of treatment, such as whether they felt fatigued. This is a far cry from reports of serious adverse events or adverse health consequences from drug treatment. Nor is it the type of effectiveness information that is likely to change in the face of new safety information about a drug. Thus, if FDA were to adopt a policy of applying the Draft PRO Guidance retroactively, this would be contrary to stated CDER policy.

Moreover, the agency has even asserted in court that it avoids retroactive application of new policies, stating that it "has generally used the filing and approval criteria in effect at the time of submission as the basis for approval of applications."[4] A federal appeals court has even held that policies issued after submission of a marketing application did not retroactively apply to a pending application. As the court recognized, "if a pending application had to be revised each time the FDA changed its regulations, the application process would become much more lengthy." *Id.*

Furthermore, the Draft PRO Guidance is focused on product development and initial product approval decisions and not on modification of existing labeling statements. *See* Draft PRO Guidance, at 1 ("By explicitly addressing the review issues identified in this guidance, sponsors can increase the efficiency of their endpoint discussions with the FDA *during the product development process*, streamline the FDA's review of PRO endpoint adequacy, and provide optimal information about the patient's perspective of treatment benefit *at the time of product approval*") (emphasis added).

FDA Has Not Issued the Final PRO Guidance

The Draft PRO Guidance is just that – a draft that is subject to change. It binds neither FDA nor industry, and would not do so even if it were final. In fact, FDA has extensive regulations that govern the guidance process, and those regulations *require* that FDA respond to comments from stakeholders before the Draft PRO Guidance is finalized and implemented. FDA adopted these regulations – and OMB has adopted them as a model for other agencies –

---

[3] Center for Drug Evaluation and Research MAPP 4000.2, *Developing and Issuing Guidance* (Sept. 2005), at 3.

[4] Reply Brief for Federal Appellants, at 18; *Serono Laboratories v. Shalala*, 158 F.3d 1313, 1323 (D.C. Cir. 1998).

because basic principles of administrative law require that the government accept comments on proposed policy, assess those comments, and publish a final policy only after taking into account public input.[5]

With respect to the Draft PRO Guidance, FDA accepted comments over a year ago, and many of those comments raise substantive and important questions about how FDA might implement the guidance. For example, the Advanced Medical Technology Association requested that FDA provide additional clarity regarding how a sponsor might demonstrate the validity of an established PRO instrument when the instrument is used in a similar but not identical patient population as an earlier study. A biotechnology manufacturer asked FDA to provide additional examples of specific concepts, such as "pain severity" used as a single rating, so that it could better design clinical trials. And, an academic commenter requested that FDA re-evaluate its future reliance on differences between PRO scores and instead focus on differences between groups.[6]

These comments demonstrate that FDA's draft, while representing substantial and worthwhile effort, still needs thoughtful analysis and revision before its implementation. The breadth and scope of the comments lead to the conclusion that it is highly likely that the agency will alter or even abandon certain principles articulated in the Draft PRO Guidance. None of the comments raised issues surrounding retroactive application because of FDA's long-standing policies against such application. Had any considered that the Draft PRO Guidance might be so applied, the objections would likely have been strenuous.

In short, it would be an imprudent use of FDA and industry resources to require companies to re-evaluate data based on a standard that very well may change again. FDA's stated policy against retroactive application would avoid this outcome and subject product labeling to only two standards – the standard in place before adoption of a final guidance and the standard finally adopted by FDA after application of its good guidance practices. But the likely result of any change in this policy would be that product labeling containing quality of life claims will have been evaluated under three different standards – pre-2006 review standards, the standard articulated in the Draft PRO Guidance, and the yet-to-be articulated standard in the final guidance.

Patients and Physicians Would Have Incomplete Information Regarding The Benefits and Risks Of Products

FDA has long recognized that patients benefit from treatment information described in comprehensive yet understandable terms. The agency requests that manufacturers of certain self-administered products provide FDA-approved patient package inserts (which accompany the full prescribing information directed towards physicians.) And it has spearheaded a private-

---

[5] *See* 21 CFR 10.115; 72 FR 3432, 3438 (Jan. 25, 2007).

[6] All comments on the Draft PRO Guidance are available for review at http://www.fda.gov/ohrms/dockets/dockets/06d0044/06d0044.htm.

sector effort aimed at providing useful written consumer medical information.[7] These efforts are aimed, in FDA's words, at the "improved dissemination of accurate, thorough and understandable information about prescription drug products . . . necessary to fulfill patients' need and right to be informed."[8]

But neither patients nor physicians would have complete information for assessing the benefits and risks of treatment if retrospective application of the Draft PRO Guidance results in *the loss* of these data from drug labeling. There is no doubt that application of standards developed in 2006 (whether referenced in guidance or not) to data and information gathered by companies in prior years would result in just that.

CONCLUSION

For all these reasons, BIO does not believe that FDA should retroactively apply the Draft PRO Guidance. Patients and physicians deserve access to quality of life data and information in order to fully assess both the benefits and risks of their treatment. And strong legal and policy considerations counsel against retroactive application of guidance documents more generally. Consequently, we request that FDA confirm its longstanding policies against the retroactive application of guidances and labeling standards, particularly with respect to previously-approved quality of life claims in drug labeling.

---

[7] *See* Public Law 104-180, Title VI, Sec 601, Effective Medication Guides, 110 Stat 1593 (1996).

[8] 60 FR 44182 (Aug. 24, 1995).