

FDA'S UNAUTHORIZED USER FEE MONEY GRAB

by

Robert A. Dormer and Kurt R. Karst

When it was enacted in 1992, the Prescription Drug User Fee Act (PDUFA), Pub. L. No. 102-571, 106 Stat. 4491 (1992), was hailed as an unprecedented accord among the Food and Drug Administration (FDA), the pharmaceutical industry, and Congress. In exchange for speedier drug approval, the industry agreed to pay user fees for certain New Drug Applications (NDAs). While PDUFA has resulted in speedier drug approvals, the cost to the industry for FDA's improved performance has increased considerably.¹ Saddled with these increasing cost burdens, FDA has apparently been forced to find new interpretations in PDUFA to offset those burdens. Nowhere is FDA's "money grab" more evident than with respect to the agency's broad and unfounded interpretation of user fee applicability to so-called 505(b)(2) applications for a new "indication for a use."

505(b)(2) applications are hybrids submitted under the Federal Food, Drug, and Cosmetic Act (FDC Act) that rely, at least in part, on investigations "not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use . . ." FDC Act § 505(b)(2). They are similar to Abbreviated NDAs (ANDAs) for generic drugs in that they may rely on FDA's previous findings of safety and effectiveness for an approved innovator drug. However, many 505(b)(2) applications are submitted either for drugs that are sufficiently different from a previously approved drug (*e.g.*, a new dosing regimen, or indication), or for a new molecular entity, so that an ANDA cannot be submitted, but for which a "full" NDA is not necessary. To obtain approval of a 505(b)(2) application, an applicant will often have to submit data, including clinical data, to demonstrate the safety and effectiveness of the change from the previously approved drug or of a new drug reported in published literature. In some 505(b)(2) applications, *e.g.*, levothyroxine, a drug for hypothyroidism and pituitary TSH suppression, the safety and effectiveness data are based entirely on published literature. In other 505(b)(2) applications, the data may be based on FDA's previous safety and effectiveness findings. The 505(b)(2) applicant must submit data that "bridges" its product to either the previously approved drug or the product reported in published literature.

Because 505(b)(2) applications are neither "full" NDAs, which require the payment of a full application user fee, nor ANDAs, for which no user fees are due, Congress created separate, and very limited conditions for when an application user fee is required. It is the authors' view that FDA has broadly interpreted the 505(b)(2) application user fee provision to require user fees far beyond anything

¹In 1992, Congress set initial user fee rates at \$100,000 (application), \$60,000 (establishment), and \$6,000 (product). The fees established for Fiscal Year 2006 are \$767,400 (application), \$264,200 (establishment), and \$42,130 (product).

Robert A. Dormer is a director, and **Kurt R. Karst** is an associate at the Washington, D.C. law firm Hyman, Phelps & McNamara, P.C.

that Congress ever intended. For example, if, at FDA's request, a 505(b)(2) applicant compared its product to a previously approved drug in a clinical trial, and if the study merely confirmed that the drug had comparable efficacy to the approved drug for the same indication, and any labeling section for the 505(b)(2) drug described the results of that study, FDA would consider the labeling change to be a new "indication for a use" and assess user fees.

PDUFA User Fees. FDA collects user fees for each "human drug application." This term is defined to mean: (1) an NDA submitted under § 505(b)(1) of the FDC Act, *see* FDC Act § 735(1)(A); and (2) a § 505(b)(2) application requesting approval of either a new molecular entity or a new "indication for a use" of a previously approved drug, *see id.* at § 735(1)(B)(i)-(ii). Applications termed "human drug applications" are subject to three types of user fees: (1) a one-time application fee; (2) an annual establishment fee; and (3) an annual product fee. *See id.* at § 736(a)(1)-(3).

505(b)(2) User Fee Applicability. Under the first criterion of § 735(1)(B), if the active ingredient has been previously approved, then the application is not a "human drug application" under this criterion. The meaning of the second criterion — a new "indication for a use" — was discussed in the legislative history of § 735(1)(B):

[FDC Act § 735(1)(B)(ii)] would limit the section 505(b)(2) applications included within the definition of "human drug application" . . . to applications that request approval of . . . an indication for a use that had not been approved under an application submitted under section 505(b). The committee intends that the term "indication" be given the meaning that it is given in the FDA's regulations, 21 C.F.R. 201.57(c), 1992. This term would include an Rx-to-OTC switch. User fees would not be required for any other new drugs approved under section 505(b)(2).²

Section 201.57 prescribes the content and format of prescription drug labeling. Subsection (c) concerns the content of the "Indications and Usage" (I&U) labeling section. Specifically, § 201.57(c) (1992) states that the I&U section must include the indications for which the drug is approved (*e.g.*, for the treatment, prevention, or diagnosis of a disease or condition), and additional information, such as available evidence supporting the safety and effectiveness of a drug only in selected subgroups, the limitations of usefulness of the drug, specific tests needed for the selection or monitoring of patients who need the drug, and information on the approximate kind, degree, and duration of improvement to be anticipated (if available). If this "information is relevant to the recommended intervals between doses, the usual duration of treatment, or any modification of dosage, it shall be stated in the 'Dosage and Administration' section of the labeling and referenced in [the I&U] section." 21 C.F.R. § 201.57(c)(3)(i). Finally, the I&U section is required to include information on certain safety considerations, specific conditions to be met before the long-term use of a drug, information on a lack of evidence that a drug is effective for a use or condition (at FDA's discretion), and any comparative safety or efficacy statements.

Neither the FDC Act nor FDA's regulations define the term "indication." However, FDA's descriptive use of the term in § 201.57(c) is consistent with the agency's application of the term to mean the "uses for a drug" or "what the drug is used for" (that is, the "indications for use"), as well as the medical dictionary definition of the term "indication."³ It is precisely these "uses for a drug" that FDA has consistently stated must be included in the I&U section, and to which Congress referred in PDUFA and the legislative history.

²Statement of Floor Managers Explaining Changes Made After Committee Consideration of H.R. 5952, 138 CONG. REC. H9099 (daily ed. Sept. 22, 1992).

³*See* [Drugs@FDA, Glossary of Terms](#); [STEDMAN'S MEDICAL DICTIONARY 892 \(26th ed. 2000\)](#).

FDA’s Broad Interpretation of a New “Indication for a Use”. Although PDUFA was enacted in 1992, the first public announcement of FDA’s interpretation of the meaning of a new “indication for a use” did not appear until April 2005 in a draft guidance document discussing FDA’s policy for waiving PDUFA user fees for certain HIV/AIDS drugs. In that document, FDA articulates a broad, and in our view unfounded, interpretation of the meaning of FDC Act § 735(1)(B)(ii):

[B]ecause only certain 505(b)(2) applications are exempt [from user fees], it is important that potential applicants who do not want to be assessed fees be advised to . . . ***not*** seek any new indications for a use. It is particularly important that they strictly follow the approved labeling for the individual ingredients. If, for example, they seek a different use of the drug, or a different dosing regimen or route of administration, or use in a new population, or compare their product to others in the labeling, they ***will not qualify*** for the 505(b)(2) exemption from fees.⁴

FDA officials have further explained this interpretation to the authors in informal communications. According to FDA, because Congress used the term “indication for a use” instead of the term “Indications and Usage,” and generally referenced § 201.57(c) in the legislative history rather than a particular portion of the regulation, substantive changes to any part of the labeling *referenced in § 201.57(c)* result in a new “indication for a use.”

Not satisfied that a new “indication for a use” means substantive changes to any part of the labeling *referenced in § 201.57(c)*, FDA more broadly applies its interpretation to mean a substantive change to *any* labeling section. Therefore, for example, if a 505(b)(2) applicant were to compare its product to a listed drug in a clinical trial, which FDA often requests 505(b)(2) applicants to do, the description of the results of that study in the labeling would be a new “indication for a use,” even if the study merely confirmed that the 505(b)(2) drug had comparable efficacy to the listed drug for the already approved indication, and even if a statement to that effect appeared only in the “Clinical Trials” labeling section.

According to FDA, the reference to Rx-to-OTC switches in the legislative history of FDC Act § 735(1)(B) further supports its broad interpretation. Instead of interpreting Congress’ statement that the term “indication” in FDC Act § 735(1)(B)(ii) “include[s] an Rx to OTC switch” to be an exception to the rule that “[u]ser fees would not be required for any other drugs approved under section 505(b)(2),” FDA interprets the exception as but one example that gives it free reign to find others. Thus, according to FDA, because in an Rx-to-OTC switch the indication remains the same, but the “indication for a use” changes (*i.e.*, Rx-to-OTC), Congress must have intended for FDA to look beyond the “Indications and Usage” section.

FDA’s tortured interpretation of Congress’s intent disassociates the meaning of a new “indication for a use” from the meaning of “indication” in § 201.57(c), and effectively severs the intended link between a new “indication for a use” and the I&U section. Untethered to changes only in the I&U section, FDA feels free to interpret any substantive labeling change as a new “indication for a use.”

FDA’s Interpretation is Misplaced. The implications of FDA’s interpretation of a new “indication for a use” are that many, if not most, 505(b)(2) applications will be termed “human drug applications,” and more user fees will be collected. However, FDA’s interpretation ignores the agency’s regulations and policies, as well as Congress’s directive.

⁴FDA, Draft Guidance for Industry: User Fee Waivers for FDC and Co-Packaged HIV Drugs for PEPFAR, at 3 (Apr. 2005) (emphasis in original).

FDA's labeling regulations at § 201.57(c) (1992) are clear: the I&U section *must* include the information stated. When it promulgated final regulations in 1979, FDA limited the meaning of "indication" to the information about the uses of a drug described and required in the I&U section. The history of § 201.57 shows that FDA has consistently upheld this limitation.

When FDA proposed the section heading "Indications and Usage" in 1975, the agency stated that "the 'Indications' section of the labeling has been changed to 'Indications and Usage,' and specific instructions have been provided for describing the indications, the optimal usage of the drug, and the limitations of use." 40 Fed. Reg. 15,392, 15,393 (Apr. 7, 1975). FDA was careful to require that all indications for uses be stated in the I&U section. For example, FDA's regulations concerning the "Pediatric Use" section stated: "A specific pediatric indication, if any, shall be described under the 'Indications and Usage' section of the labeling." 21 C.F.R. § 201.57(f)(9) (1992).

When § 201.57 was amended in 1994 and 1997, FDA once again affirmed that all indications for uses must be stated in the I&U section. Section 201.57(f)(9) ("Pediatric Use") was amended to state: "If there is a specific pediatric indication . . . it shall be described in the 'Indications and Usage' section." 21 C.F.R. § 201.57(f)(9)(ii). Similarly, § 201.57(f)(10) ("Geriatric Use") states: "A specific geriatric indication . . . shall be described under the 'Indications and Usage' section of the labeling." *Id.* at § 201.57(f)(10). Finally, when it issued a proposed rule in 2000 to revise § 201.57(c), FDA specifically proposed to include the following statement in the I&U section: "Indications or uses must not be implied or suggested in other sections of labeling if not included in this section." 65 Fed. Reg. 81,082, 81,115 (Dec. 22, 2000) (quoting proposed § 201.57(c)(2)(ii)). FDA has not yet issued final regulations.

Based on the clear meaning of "indication" in § 201.57(c) and FDA's requirements that all indications for uses appear in the I&U section, Congress linked the term "indication for a use" with the information in the I&U section. Therefore, if the information required by § 201.57(c) is not stated in the I&U section, it is not the type of information Congress referred to in the legislative history as supporting a new "indication for a use." Had Congress intended a broader interpretation of a new "indication for a use" that applied to all labeling statements, and as FDA has unconvincingly interpreted Congress's intent, Congress would have expressed that intention. But it did not. Rather, Congress considered the scope of information FDA requires to appear in the I&U section and carefully limited FDA's ability to apply user fees to changes only in that labeling section. FDA's interpretation of congressional intent is misplaced and without merit.

Even FDA's attempt to justify its broad interpretation of a new "indication for a use" with respect to Rx-to-OTC switches is contrary to agency policy. FDA specifically defines in its draft 505(b)(2) guidance a 505(b)(2) application for an Rx-to-OTC switch as "[a]n application to change a prescription indication to an [OTC] indication." FDA, Draft Guidance for Industry, Applications Covered by Section 505(b)(2), (Oct. 1999) at 5.⁵ Thus, an Rx-to-OTC switch is, in fact, a change in indication; and the exception cited by Congress is consistent with changes in the I&U section.

Conclusion. FDA has adopted a tortured interpretation of the term a new "indication for a use" that violates the accord reached with Congress and the pharmaceutical industry in 1992. A commonsense interpretation of a new "indication for a use" means exactly what Congress said it means: any new indication for a drug not previously approved that appears in the I&U section. FDA would be wise to reevaluate its overbroad interpretation.

⁵When FDA approved a 505(b)(2) application for an Rx-to-OTC switch of loratadine, the indication changed from "for the relief of nasal and non-nasal symptoms of seasonal allergic rhinitis" to "for the temporary relief of symptoms of hay fever or other respiratory allergies: nasal congestion, runny nose, sneezing, itchy, watery eyes, and itching of the nose or throat." FDA, Approval Letter, NDA #21-375, at 1 (Dec. 19, 2002).