



THE DRUG USER FEE CATCH-22

by

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In August 2005, the authors wrote a Washington Legal Foundation LEGAL BACKGROUNDER¹ on the Food and Drug Administration's (FDA's) broad interpretation of a provision added to the Federal Food, Drug, and Cosmetic Act (FDC Act) by the Prescription Drug User Fee Act (PDUFA), Pub. L. No. 102-571, 106 Stat. 4491 (1992), concerning the applicability of user fees to 505(b)(2) applications for a new "indication for a use." Subsequent to that paper's release, Congress passed The FDA Amendments Act (FDAAA), Pub. L. No. 110-85, 121 Stat. 823 (2007). The law reauthorized PDUFA through Fiscal Year 2012 and eliminated the distinction between 505(b)(1) and 505(b)(2) New Drug Applications (NDAs) for user fee purposes. Under the new law, all 505(b)(2) applications are *fee-paying* applications. Abbreviated NDAs (ANDAs) for generic versions of drug products approved under FDC Act § 505(b) are not subject to PDUFA user fees. Although FDA's broad pre-FDAAA interpretation of the FDC Act required many (if not most) 505(b)(2) applicants to pay user fees, a change in inactive ingredients to the drug product formulation would qualify a 505(b)(2) application as a fee-paying application *if* such a change altered drug product labeling in a way that created a new "indication for a use."

FDA's regulations preclude the submission of an ANDA for certain drug product category inactive ingredient changes – so-called "non-exception excipients" – unless the Agency waives such regulations under 21 C.F.R. § 314.99(b). Historically, FDA policy limits granting such waivers to cases in which an ANDA applicant seeks approval to market a drug product containing a non-exception excipient used in a discontinued, brand-name Reference Listed Drug (RLD) formulation that is not used in the currently-marketed RLD formulation. As a result, manufacturers unable to obtain a waiver for a non-exception excipient change are effectively forced to submit a 505(b)(2) application. While under the pre-FDAAA PDUFA law, such an application usually would *not* have qualified as a fee-paying application, the changes made to PDUFA under FDAAA require the payment of user fees by all FDC Act § 505(b) applicants. In short, such applicants become the victims of a "Catch-22." That is, FDA's unnecessarily narrow non-exception excipient policies preclude the submission and approval of an ANDA, which is not subject to PDUFA user fees, and effectively force the submission of a 505(b)(2) application. Meanwhile, Congress' decision in passing FDAAA to make all 505(b)(2) applications fee-paying applications means that such applications are subject to user fees, which are quite substantial. For Fiscal Year 2009, the one-time full application fee is \$1,247,200, and annual product and establishment fees are \$71,520 and \$425,600 respectively. These fees will likely rise in the coming years.

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FDA's Exception Excipient Regulations. Section 505(j)(4)(H) of the FDC Act states that FDA must approve an ANDA unless, among other things:

information submitted in the application or any other information available to [FDA] shows that (i) the inactive ingredients of the drug are unsafe for use under the conditions prescribed, recommended, or suggested in the labeling proposed for the drug, or (ii) the composition of the drug is unsafe under such conditions because of the type or quantity of inactive ingredients included or the manner in which the inactive ingredients are included.

FDA's regulations implementing FDC Act § 505(j)(4)(H) generally are found in the Agency's ANDA content and format regulations at 21 C.F.R. § 314.94. Pertinent regulations on inactive ingredient changes for certain types of generic drug products are set forth in 21 C.F.R. § 314.94(a)(9). For example, FDA's regulations for parenteral drug products at 21 C.F.R. § 314.94(a)(9)(iii) state:

Generally, a drug product intended for parenteral use shall contain the same inactive ingredients and in the same concentration as the [RLD] identified by the applicant under paragraph (a)(3) of this section. However, an applicant may seek approval of a drug product that differs from the reference listed drug in preservative, buffer, or antioxidant provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.

Preservative, buffer, and antioxidant changes in generic parenteral drug products are referred to as "exception excipients," which may qualitatively or quantitatively differ from the RLD formulation. Other regulations at § 314.94(a)(9)(iv) identify exception excipients for generic ophthalmic and otic drug products (*i.e.*, preservative, buffer, substance to adjust tonicity, and thickening agent). Excipients not identified in these regulations are referred to as "non-exception excipients."

FDA's exception excipient regulations at § 314.94(a)(9) find their parallel in 21 C.F.R. § 314.127(a)(8)(ii), which addresses the grounds for an FDA refusal to approve an ANDA for a parenteral, ophthalmic, or otic drug product. For example, § 314.127(a)(8)(ii)(B) states: "FDA will consider an inactive ingredient in, or the composition of, a drug product intended for parenteral use to be unsafe and will refuse to approve the [ANDA] unless it contains the same inactive ingredients, other than preservatives, buffers, and antioxidants, in the same concentration as the listed drug. . . ."²

Surprisingly, there is no explanation in the preambles to either the 1989 proposed rule or the 1992 final rule for the above-referenced regulations for including the exception excipients or excluding other types of inactive ingredients, nor did FDA provide any explanation in the Agency's now-abandoned November 1994 Interim Inactive Ingredients Policy.

FDA's Exception Excipient Regulations and Waiver Policy are Unnecessarily Narrow and Legally Flawed. When FDA promulgated its exception excipient regulations in 1992, the Agency noted that with respect to 21 C.F.R. § 314.127, the inquiry under the FDC Act is whether a change in an inactive ingredient is "safe under the conditions prescribed, recommended, or suggested in the labeling," and that the regulation reflects this concern. *See* FDA, Final Rule, Abbreviated New Drug Regulations, 57 Fed. Reg. 17,950, 17,970 (Apr. 28, 1992). Thus, differences in inactive ingredients are not a basis for refusing to receive or approve an ANDA under the FDC Act, unless FDA has reason to believe that the inactive ingredients in the proposed generic drug "are unsafe" or that the composition of the proposed generic drug "is unsafe . . . because of the type or quantity of inactive ingredients included or the manner in which the inactive ingredients are included." FDC Act § 505(j)(4)(H).

FDA's ANDA regulations concerning inactive ingredient changes in parenteral, ophthalmic, and otic drug products are not to the contrary. FDA's regulations require that an ANDA "contain[] sufficient information to demonstrate that the difference [in inactive ingredient(s)] does not affect the safety or efficacy of the drug product." 21 C.F.R. § 314.127(a)(8)(ii)(B) (parenteral). Similarly, FDA's ANDA format and content regulations state that an ANDA applicant must "identif[y] and characterize[] the [inactive ingredient] differences and provide[] information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product." *Id.* at § 314.94(a)(9)(iii) (parenteral). Although the regulations single out certain excipients, it is illogical to interpret the specific categories as exclusive, thereby precluding changes in other inactive ingredients that have no effect on the safety of the generic drug.³ Further, if that interpretation were applied as a ground for refusing to receive or approve an ANDA, it would be inconsistent with FDC Act § 505(j)(4)(H). Therefore, the list of excipients in FDA's ANDA regulations should be appropriately interpreted as illustrative rather than exhaustive of the changes in inactive ingredients that are permitted if the lack of a safety or efficacy effect is demonstrated.⁴

Notwithstanding FDA's exception excipient regulations, the Agency has, on occasion, but only in very limited circumstances, waived these regulations to permit the receipt and approval of an ANDA for a drug product containing a non-exception excipient change from the RLD.

Agency regulations at 21 C.F.R. § 314.99(b) state that a generic applicant "may ask FDA to waive . . . any requirement that applies to the applicant under §§ 314.92 through 314.99. The applicant shall comply with the requirements for a waiver under § 314.90." The parallel waiver regulation for 505(b) applicants, section 314.90, describes the information an applicant must submit to support a waiver request, and states that FDA may grant a waiver if the Agency finds: "(1) the applicant's compliance with the requirement is unnecessary for the agency to evaluate the application or compliance cannot be achieved; (2) the applicant's alternative submission satisfies the requirement; or (3) the applicant's submission otherwise justifies a waiver." 21 C.F.R. § 314.90(b). Pursuant to this waiver regulation, FDA may waive its ANDA exception excipient regulations under 21 C.F.R. 314.99(b) so that the Agency can receive and approve an ANDA.

FDA has granted a § 314.99(b) waiver when an ANDA applicant seeks approval to market a drug product containing a non-exception excipient used in a discontinued RLD formulation that is not used in the currently-marketed RLD formulation. For example, FDA has allowed applicants seeking approval to market generic Sandostatin (octreotide acetate) Injection to substitute a different tonicity agent (a non-exception excipient change) and buffer system because "the inactive ingredients (including the buffer system and tonicity agent) used in the discontinued formulation of Sandostatin do not make that formulation unsafe. . . [and because] the discontinued formulation of Sandostatin is no less safe and effective than the new formulation." FDA, Response, Docket No. FDA-2005-P-0370, at 6 (Mar. 25, 2005). By granting § 314.99(b) waivers, FDA arguably furthers a goal of the Hatch-Waxman Amendments – to help "make available more low costs generic drugs" – by, among other things, rewarding applicants for challenging and designing around patents on brand name drugs.⁵

The agency's actions in the publicly known waiver cases to date are commendable and are in accordance with the FDC Act. FDA's policy, however, of limiting § 314.99(b) waivers to cases involving discontinued RLD formulations, thereby precluding waivers in other factually compelling cases has no basis in the FDC Act. The inquiry under the FDC Act is whether an excipient in a proposed generic drug product is "[safe] for use under the conditions prescribed, recommended, or suggested in the labeling proposed for the drug, or [whether] the composition of the drug is unsafe under such conditions because of the type or quantity of inactive ingredients included or the manner in which the inactive ingredients are included." FDC Act § 505(j)(4)(H). If the statutory inactive ingredient standard is met (among other requirements), then "FDA shall approve" the proposed ANDA. *Id.* at § 505(j)(4).

While § 314.99(b) waiver cases involving discontinued formulations may be cases in which FDA

can very easily determine whether the inactive ingredients in a generic formulation are safe, such cases do not represent the universe of scenarios in which the Agency can make similar determinations and grant a waiver. When the safety of a non-exception excipient in a proposed generic formulation is known or readily apparent (*e.g.*, because it is listed in FDA’s Inactive Ingredient Database or reported on in the published literature), then FDA should (at a minimum) grant a § 314.99(b) waiver to receive the application. Indeed, FDC Act § 505(j)(4)(H) presumes that the Office of Generic Drugs will receive and approve an ANDA unless “information submitted in the [ANDA] or any other information available to [FDA] shows that” the proposed inactive ingredient is “unsafe.” FDC Act § 505(j)(4)(H). This position is consistent with FDA’s citizen petition response regarding a non-exception excipient change concerning generic Sandostatin Injection. FDA’s response repeatedly states that because an ANDA containing a non-exception excipient in a discontinued formulation “would clearly *meet the statutory standard* for approval under [FDC Act § 505(j)(4)(H)], the Agency may rely on [§] 314.99(b) to grant a waiver of [§ 314.94(a)(9)(iii)].” FDA Response, Docket No. FDA-2005-P-0370, at 8 (emphasis added). Thus, FDA has acknowledged, as it must, the primacy of FDC Act § 505(j)(4)(H) over the Agency’s ANDA excipient regulations, and has recognized that the inconsistency between the broad statutory language and the narrow regulatory language can be remedied by granting a § 314.99(b) waiver.

Conclusion. FDA’s artificial limitation – both in its ANDA excipient regulations and in its § 314.99(b) waiver policy – is unfounded and inconsistent with the clear language of FDC Act § 505(j)(4)(H). Moreover, interpreting § 314.94(a)(9) to represent an exhaustive list rather than an illustrative list of permissible excipient differences renders the regulations in conflict with FDC Act § 505(j)(4)(H). Agencies may not implement their rules and regulations in a manner that conflicts with the statute. Of course, FDA could avoid a conflict between FDC Act § 505(j)(4)(H) and its exception excipient regulations by interpreting the list of excipients in its regulations as illustrative rather than as exhaustive, or by granting § 314.99(b) waiver requests for non-exception excipients outside of discontinued RLD formulation scenarios, provided there is sufficient information to show that an excipient in a proposed drug product is safe for use. By doing so, a generic applicant would be able to submit an ANDA, rather than being effectively forced to submit a user fee-paying 505(b)(2) application, and could avoid the Catch-22 Congress created with FDAAA.

¹See Robert A. Dormer, Kurt R. Karst, *FDA’s Unauthorized User Fee Money Grab*, LGL BACKG. (Wash. Lgl Found.) Vol. 28, No. 30 (Aug. 12, 2005) available at <http://www.wlf.org/upload/081205LBDormer.pdf>.

²In addition, although not as explicit as FDA’s refusal to approve regulations, § 314.101(d)(3) provides that FDA may refuse to receive an ANDA if the application is incomplete because, among other things, it does not contain information required under § 314.94.

³In fact, FDA has stated that “[t]he regulations [on excipient changes] seem intended to address the use of excipients that could not be adequately addressed in the ANDA context (i.e., unfamiliar excipients, or excipients of a type more likely to raise safety concerns for parenteral drugs).” FDA, Response, Docket No. FDA-2005-P-0370, at 7 (Mar. 25, 2005).

⁴It is noteworthy that other aspects of FDA’s 1992 ANDA regulations have been struck down by the courts because, as here, an actual conflict exists between the FDC Act and the Agency’s implementing regulations. See, *e.g.*, *Mova Pharm. Corp. v. Shalala*, 140 F.3d 1060 (D.C. Cir. 1998) (invalidating FDA’s “successful defense” requirement); *Mylan Pharmaceuticals, Inc. v. Shalala*, 81 F. Supp. 2d 30 (D.D.C. 2000) (invalidating FDA’s regulation defining “court decision”). Similarly, FDA’s exception excipient regulations might be susceptible to a procedural challenge.

⁵H.R. Rep. No. 857, 98th Cong. 1st Sess., pt. 1, at 14 (1984), reprinted in 1984 U.S.C.C.A.N. 2647; see also *Mead Johnson Pharm. Group v. Bowen*, 838 F.2d 1332, 1333 (D.C. Cir. 1988) (“The purpose of [the Hatch-Waxman Amendments] is to increase competition in the drug industry by facilitating the approval of generic copies of drugs.”).