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A fight left unfinished — the D.C. Circuit in *Takeda v. Burwell* declines to clarify the scope of Hatch-Waxman Paragraph IV certifications

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On July 15, 2016, the D.C. Circuit Court of Appeals held that Takeda Pharmaceuticals' challenge to the U.S. Food and Drug Administration's (FDA) decision to approve Hikma Pharmaceuticals' competing gout drug, Mitigare, was mooted by a recent ruling in the parties' related litigation that Hikma did not infringe Takeda's patents. As a prerequisite to FDA approval of Hikma's new drug application (NDA) under Section 505(b)(2) of the Hatch-Waxman amendments to the Food, Drug, and Cosmetic Act,[1] Hikma was required to choose a reference listed drug (RLD) and certify that patents covering that drug whose safety or other data Hikma "relied upon" for FDA approval are "invalid or will not be infringed by the manufacture, use, or sale of [its] new drug"—a so-called "Paragraph IV" certification. *See* 21 U.S.C. § 355(b)(2)(A)(iv). Unlike an initial (or "innovator") NDA, a Section 505(b)(2) NDA applicant can rely on studies submitted to FDA by third-parties in support of a previously approved RLD to help demonstrate that the applicant's drug is safe and effective. Hikma did just that, but rather than expressly refer to Takeda's gout drug, Colcrys, Hikma identified an older drug, Col-Probenecid—the same listed drug Takeda relied on for approval of its application for Colcrys. While Takeda asserts patent protection over Colcrys, no patent protection remains for Col-Probenecid. Hikma's approach allowed it to sidestep the need to certify that Mitigare did not infringe Takeda's patents covering Colcrys despite FDA's own apparent reliance on Colcrys-related data for its approval of Hikma's application.

Takeda argued that Hikma intentionally "gerrymandered" its application to bypass this requirement and that FDA's decision to allow Hikma to do so was arbitrary and capricious for purposes of the Administrative Procedure Act, thereby wrongfully delaying a statutory stay of Hikma's drug application pending patent litigation. In Takeda's view, FDA "emptied [Section

[1] The Section 505(b)(2) approval pathway is designed to allow the approval of a drug that isn't new, but differs in several meaningful aspects from previously approved drugs. As described in the FDA's 1999 guidance document, Applications Covered by Section 505(b)(2), a 505(b)(2) application "[I]s one for which one or more of the investigations relied upon by the applicant for approval 'were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.'" This so-called "paper NDA" pathway to approval has become increasingly popular in recent years.

505(b)(2)] of effect by permitting an applicant to certify only to those drugs expressly named in its application—even if FDA uses an unnamed drug's data to approve the application." That permissive certification, Takeda argued, "is inconsistent with the statutory text, with common sense[] and with FDA's longstanding interpretation that an applicant must certify to any drugs without which 'the application cannot be approved.'" Based on FDA's extensive reference to Colcrys in the administrative record, Takeda contended that its Colcrys-related data was, in fact, necessary to Mitigare's approval and, thus, Hikma should have been required to issue Paragraph IV certifications for Takeda's patents covering Colcrys.

The dispute was but a skirmish in the larger war between these two fierce competitors, but posed a very interesting and important question to the D.C. Circuit—what are the precise bounds of the Paragraph IV certification requirement in the context of a 505(b)(2) application? Is that obligation, and the hypothetical act of infringement it generates, strictly tied to the data an applicant chooses to refer FDA to or is it broader? After all, the statutory construct is designed to bring to the fore inevitable patent disputes among competing drug makers, dampening market disruptions in the process and accelerating the availability of affordable generic alternatives. Why should an applicant be able to avoid bringing patents covering very similar, if not identical, drugs into the fray? Is it not more efficient to require that they do so? Or is that simply an applicant's prerogative, left perhaps to balance the strength of its application against the invocation of a mandatory stay and delay of product launch?

These are all interesting questions that the D.C. Circuit left unanswered. After learning of Hikma's drug application, Takeda had already initiated a separate patent infringement suit in the District Court of Delaware. In May 2016, the District Court dismissed Takeda's claims and ruled that Hikma had not infringed Takeda's patents. Any potential gain from unwinding FDA's approval (e.g., requiring a new or extended stay) was now, the D.C. Circuit reasoned, unavailable as a matter of law.[2] The ultimate issue the stay is designed to most efficiently present—patent validity and infringement—had been decided by the District Court. While Takeda argued about who did or should have thrown the first punch and when, simply put, the outcome of the bout had been decided. Left wanting more, observers of this sweet-science (meaning ANDA litigation of course) will just have to wait for the next bout.

That is unless FDA's long-awaited guidance on this issue is finalized in the meantime. In early 2015, FDA published a proposed rule "intended to help ensure that the 505(b)(2) pathway is not used to circumvent the statutory patent certification obligations," that require 505(b)(2) applicants "to identify a pharmaceutically equivalent product, if already approved, as a listed drug relied upon." While pharmaceutical equivalence arguably draws a murky line, it offers some guidance to 505(b)(2) applicants regarding the scope of their Paragraph IV certification obligations. FDA has not yet promulgated a final version of the rule. Instead, FDA has continued to extend the rule's comment period on multiple occasions, most recently through June 2016.

A copy of the D.C. Circuit's decision in its entirety is available here. A copy of FDA's proposed rule is available here.

[2] In addition, Takeda argued the FDA acted arbitrarily and capriciously in approving Hikma's Section 505(b)(2) application without requiring that Mitigare's label include safety information related to dosage that the FDA previously required for similar formulations. The D.C. Circuit paid the argument little mind, declining to revisit the FDA's "scientific judgments."

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