Portfolio Media. Inc. | 111 West 19th Street, 5th Floor | New York, NY 10011 | www.law360.com
Phone: +1 646 783 7100 | Fax: +1 646 783 7161 | customerservice@law360.com

Highlights Of The FDA's Abbreviated New Drug Applications


John R. Manthei


J. Benneville Haas


Amy E. Speros


Morgan A. Rettig

Law360, New York (October 11, 2016, 4:14 PM EDT) -- On Oct. 6, 2016, the U.S. Food and Drug Administration published a 79-page final rule in the Federal Register, revising its regulations governing the requirements for submission and approval of abbreviated new drug applications (ANDAs) submitted under Section 505(j) of the Federal Food, Drug, and Cosmetic Act (FDCA) and New Drug Applications (NDA) submitted under Section 505(b)(2) of the FDCA (505(b)(2) applications).[1] The final rule finalizes a comprehensive proposed rule that was published on Feb. 6, 2015 (the proposed rule),[2] and in response to which the FDA received 13 comment letters. According to the FDA, the final rule implements portions of Title XI of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA) by formalizing many agency policies developed over its 13 years of implementing the statute, while also revising and clarifying FDA's existing regulations on ANDAs and 505(b)(2) applications. Notably, the final rule does not address issues related to the circumstances under which an ANDA applicant may be deemed to have forfeited 180-day exclusivity under Section 505(j)(5)(D) of the FDCA. The FDA instead states that it will continue to implement those provisions of the MMA directly from the statute, and may issue a separate rule at a later date.

This news flash reviews the highlights of the FDA's final rule, but is not intended to be a summary of all of the rule's provisions. Clients should consult counsel with any questions about the content or application of the rule.

Submission of Patent Information

The final rule contains a number of provisions pertaining to the procedures and requirements for NDA holders to submit information about their patents to the FDA for inclusion in the FDA's List of Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"). Many of these provisions codify or clarify the FDA's existing practice, but a few are noteworthy — namely, those pertaining to the submission of information about original and reissued method-of-use patents.

Submission of Use Codes for Method-of-Use Patents

Under the FDA's current regulations, NDA holders are required to submit information for each method-of-use patent claiming the approved drug to the FDA for inclusion in the Orange Book.[3] This information is known as the "use code." The FDA's current regulations require that NDA holders, when submitting a use code, "shall separately identify each pending or approved method of use and related patent claim."[4] In the preamble to the FDA's proposed rule, the agency stated that, because a particular method-of-use might involve multiple claims, this text "has been subject to differing

interpretations by applicants" as to whether it requires submission of patent information on a claim-by-claim basis.[5] The preamble clarified that under the FDA's current and longstanding interpretation, the NDA holder must identify individual patent claims for a method-of-use patent in order to assist ANDA and 505(b)(2) applicants (together, follow-on applicants) in determining whether a listed patent claims a use for which the applicant is seeking approval.[6] If the applicant is seeking approval for a use claimed by a listed method-of-use patent, the applicant must submit a patent certification with its application — such as a paragraph IV certification stating that the patent is invalid or will not be infringed by the application. Submission and notice of a paragraph IV certification, in turn, provides the NDA holder and/or patent holder with an opportunity to file a patent infringement suit and initiate a 30-month stay on the FDA's approval of the follow-on application. However, if the applicant is not seeking approval for a use claimed by a listed method-of-use patent (by, for example, carving out the protected use from the proposed labeling), the applicant can instead submit a "section viii" statement indicating that the patent does not pose a bar to the approval of the application "because the applicant seeks to market the drug for a use other than the one encompassed by the patent."[7] The FDA emphasized that if the method-of-use patent listing that the NDA holder submits to the FDA is not claim-specific, there might be no way to tell from that listing whether the uses for which the follow-on applicant seeks approval are separate from or overlap with the uses covered by the method-of-use patent.[8]

This situation is complicated further because the FDA has taken the position that, in determining whether a follow-on applicant's section viii statement properly carves out all uses covered by the applicable method- of-use patent, the FDA does not have jurisdiction to independently assess the NDA holder's description of the claimed use(s). Instead, the FDA must reject any section viii statement if any of the uses proposed by the follow-on applicant overlap with the use code submitted by the NDA holder. The proposed rule noted, quoting from the Supreme Court's decision in Caraco Pharmaceutical Laboratories Ltd. v. Novo Nordisk A/S, 132 S. Ct. 1670, 1684 (2012), that "[a]n overbroad use code ... throws a wrench into the FDA's ability to approve generic drugs as the statute contemplates" because an overbroad use code could prevent the FDA from approving a follow-on application even if the application seeks approval for a use that does not overlap with any of the uses claimed by the patent.

To address this problem, the FDA has interpreted its use code listing regulations to require that each claim of a pending or approved method of use patent must be separately identified on the submission form along with the patent claim number(s). According to the FDA, this separate identification of each patent claim facilitates the FDA's ability to assess section viii carve-out statements submitted in follow-on applications.[9] The proposed rule also sought to require patent holders to "identif[y] the specific section(s) of the proposed labeling for the drug product that corresponds to the method of use claimed by the patent submitted[.]"10 Finally, the proposed rule proposed to add an express provision requiring that the use code "contain adequate information to assist 505(b)(2) and ANDA applicants in determining whether a listed method-of-use patent claims a use for which the 505(b)(2) of ANDA applicant is not seeking approval" and provided the example that "if the scope of the method-of-use claim(s) of a patent does not cover every use of the drug, the applicant must only identify the specific portion(s) of the indication or other condition of use claimed by the patent." 11 The preamble explained that these provisions were intended to ensure satisfaction of the longstanding requirement that the patent-holder's use code submission contain adequate information to assist FDA and follow-on applicants in determining whether the use for which a follow-on applicant is seeking approval is actually claimed by a listed method-of-use patent, as well as to facilitate the FDA's evaluation of whether the omission of aspects of the listed drug's labeling protected by patent would render the proposed follow-on drug less safe or effective than the listed drug for all remaining non-protected conditions of use and, therefore, preclude approval.[12]

Notably, a number of commenters took issue with the failure of the proposed rule to resolve the ambiguities that exist under the FDA's current practice. Nonetheless, in the final rule, the FDA largely adopted the provisions of the proposed rule with only minor clarifying changes. The most notable of these changes is that, in lieu of the above mentioned example of the type of information that might be

adequate to assist 505(b)(2) and ANDA applicants in determining whether a listed method-of-use patent claims a use for which the applicant is not seeking approval, the final rule provides a modified example: "if the scope of the method-of-use claim(s) of a patent does not cover an indication or other approved condition of use in its entirety, then the applicant must describe only the specific approved method of use claimed by the patent for which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product."[13] While this change does provide some additional clarity, it leaves open some questions about the extent of the NDA holder's responsibility to predict the types of patent infringement claims that a follow-on applicant might assert.

The FDA also provides "general principles" for the content of use codes in three situations: where the patented method of use is (a) broader than the product approval (the use code would need to be phrased more narrowly than the patent claim to describe the specific patented method-of-use that is described in FDA-approved product labeling); (b) coextensive with the product approval (the use code must describe only the specific approved method of use claimed by the patent); and (c) narrower than the product approval (the use code must describe only the specific approved method of use claimed by the patent — not the broader indication or other approved condition of use that may include, but is broader than, the use claimed by the patent).[14] These clarifications are unlikely to provide much additional clarity for NDA holders.

Submission of Use Code Amendments

The final rule also clarifies when an NDA holder's submission of an amendment that changes a use code would be considered untimely filing of patent information, such that sponsors of pending follow-on applications would not be required to certify or recertify to the associated method-of-use patent. Under the final rule, an NDA holder's amendment to the description of the approved method(s) of use claimed by a patent will be considered timely filed if it submitted within 30 days of: (a) patent issuance; or (b) approval of a corresponding change to product labeling; or (c) a decision by the U.S. Patent and Trademark Office or a federal court that is specific to the patent and alters the construction of one or more method-of-use claim(s) of the patent.[15] By default, such an amendment will be considered untimely filed in all other circumstances. The FDA added the last of these timely filed circumstances (USPTO or federal court decision) in response to comments on the proposed rule. The FDA, however, declined to broaden the scope of the provision to allow for use code changes to be considered timely filed based on changes in patent law or interpretation that are not specific to the patent for which the particular use code was submitted.[16]

Submission of Information on Reissued Patents

In one of the most notable reversals from the proposed rule, the FDA's final rule abandons the proposal to treat an original and reissued patent as a "single bundle of patent rights" for purposes of the patent holder's submission of patent information. For context, FDA regulations require that NDA holders submit patent information for listing in the Orange Book within 30 days of approval of the NDA, and for patents issued after the date of approval, within 30 days of issuance of the patent.[17] In the proposed rule, the FDA had proposed that a reissued patent would automatically be treated as late-listed relative to a particular ANDA or 505(b)(2) application if the original patent was late-listed relative to that application.[18] As a result, if the original patent was late-listed, the follow-on applicant would not have been required to submit (or resubmit) a patent certification or statement for the reissued patent, even if the patent holder timely filed the reissued patent in the Orange Book, because sponsors of follow-on applications that are pending at the time of patent listing are not required to certify to late-listed patents.[19]

Commenters to the proposed rule noted that the FDA's proposal to treat an original patent and reissue of that patent as a "single bundle" of patent rights contravened a Dec. 16, 2014, decision from the

Fourth Circuit in Mylan Pharmaceuticals Inc. v. U.S. Food and Drug Administration, 594 F. App'x 791 (4th Cir. Dec. 16, 2014), which held that the FDA's use of the single bundle of patent rights interpretation to prevent a follow-on applicant from submitting a Paragraph IV certification to a reissued patent, which in turn foreclosed the applicant from eligibility for 180-day exclusivity violated the pre-MMA provisions of the FDCA. In the final rule, the FDA agreed with these comments and concluded that "the Agency now considers reissued patents as separate and distinct from the original patent for purposes of administering the patent certification requirements of the FD&C [Federal Food, Drug, and Cosmetic] Act and any 30-month stay of approval or 180-day exclusivity."[20]

Also resulting from that change in position, the FDA declined to finalize a provision of the proposed rule concerning the effect of patent reissuance on the eligibility of ANDA applicants for 180-day exclusivity. Under the final rule, the FDA will evaluate eligibility for 180-day exclusivity based on whether the criteria are met for an original patent (irrespective of whether the patent is subsequently reissued) or for a reissued patent.[21]

Method-Of-Use Patent Listing Disputes

One of the most controversial provisions of the proposed rule concerned a proposed process for resolving disputes between NDA holders and third parties (such as potential follow-on applicants) regarding listed use codes for method-of-use patents. The proposed rule would have required any person disputing the accuracy or relevance of a use code published in the Orange Book to notify the FDA in writing of the dispute along with the grounds for the disagreement. The FDA would then have asked the NDA holder, within 30 days, to confirm the correctness of the use code and provide information on the specific approved use claimed by the patent to enable the agency to make a determination. If the NDA holder did revise the use code in response to the request, the follow-on applicant would have been required to include an appropriate certification for the relevant method-of-use patent in its application, regardless of any disagreement as to the correctness of the use code. However, if, in the FDA's view, there was insufficient information to make a determination and the NDA holder had confirmed the correctness of its description of the specific approved use claimed by the patent, the FDA would have reviewed the proposed labeling for the follow-on drug with deference to the follow-on applicant's interpretation of the scope of the patent.[22]

In effect, this provision would have provided deference to a follow-on applicant with respect to its interpretation of the scope of the method of use claimed by a listed patent in situations where that same follow-on applicant is seeking to carve out the protected conditions of use from its product label in order to avoid certifying to the patent. While the FDA expressed that its intent in providing this benefit to follow-on applicants was to address the problem of overbroad and ambiguous use codes, which can serve to delay approval of follow-on products,[23] this provision could have had the effect of tipping the scale substantially in the other direction.

Apparently recognizing the potential wide-ranging consequences of this provision, the FDA declined to finalize its proposal in the final rule, though it left open the possibility of establishing such a process in the future. The FDA stated that it "intend[s] to take a stepwise approach and evaluate whether FDA's revisions to the regulations on submission of method-of-use patent information ... and patent listing dispute procedures adequately address the problem of overbroad and ambiguous use codes before [it] establish[es] a process to review a proposed labeling carve-out with deference to the 505(b)(2) and/or ANDA applicant(s)' interpretation of the scope of the patent."[24] The FDA also affirmed that it believes it has the authority to establish a scheme under which the FDA would defer to the follow-on applicant's interpretation of the scope of a patent that the applicant does not own.[25]

That said, the final rule does permit third parties to dispute the accuracy or relevance of patent information in the Orange Book by submitting a written request to the FDA. The FDA will send the written request to the applicable NDA holder without review or redaction, and, within 30 days, the

patent holder is required to submit a narrative response to the dispute, verify the accuracy and completeness of the use code or withdraw or amend it, and submit a signed verification that the information submitted is accurate and complete under penalty of perjury (under 21 C.F.R. § 314.53(c)(2)(ii)(R)).[26] If the patent holder timely responds, the FDA will retain or amend the use code in the Orange Book in accordance with the response (and any amended patent information submitted in accordance with these procedures will not be considered untimely filed patent information).[27] Notably, the final rule does not describe what happens if the patent holder does not timely respond, leaving open the varying possibilities that the FDA could amend the patent listing to conform to the third party's interpretation, or retain the patent listing as is.

Timing of Paragraph IV Certification Notices

In another controversial provision, the proposed rule sought to establish a date before which follow-on applicants may not provide notice of a paragraph IV certification for a listed patent to the NDA holder and/or patent holder: "the first working day after the day the patent is published in the Orange Book."[28] In the preamble to the proposed rule, the FDA explained that this proposed change stemmed from the agency's concern about ANDA applicants using "serial submissions" of paragraph IV certifications and multiple paragraph IV notices to the patent-holder during the time between patent grant and listing in the Orange Book.[29] According to the FDA, these practices are utilized in order to secure ANDA first-filer status and the associated 180-day marketing exclusivity.[30] The FDA stated that these practices, however, impose a heavy burden on both industry and the FDA, and create a potentially unequal playing field between and among ANDA applicants.[31]

The FDA finalized this provision in the final rule, rejecting commenter assertions that this "leveling the playing field" would dilute the value of 180-day exclusivity.[32]

The FDA also finalized a provision of the proposed rule specifying that a paragraph IV notice must be sent not later than 20 days after the date of the postmark on the paragraph IV acknowledgment letter to be considered timely, implementing an express provision of the MMA.[33] Notably, however, the FDA did not finalize its prior proposal to impose administrative consequences on ANDA applicants that fail to provide timely notice of a paragraph IV certification. In the proposed rule, the FDA had proposed that if the FDA determines that an ANDA applicant did not send timely notice of a paragraph IV certification, the FDA would deem the date that the ANDA was submitted to be delayed by the number of days by which the timeframe for sending the paragraph IV notice was exceeded, which could have potentially caused such ANDA applicants to lose first-applicant status and eligibility for 180-day exclusivity.[34] The FDA declined to finalize this provision in the final rule, stating that it was unnecessary in light of other incentives for ANDA applicants to provide timely notice.[35] The FDA noted that commenters challenged the FDA's authority to impose such an administrative consequence, but rejected that basis for declining to finalize the provision.[36]

Patent Certification Requirements for Amendments and Supplements to Follow-On Applications

Also somewhat controversial were provisions of the proposed rule that would have altered the patent certification requirements for amendments and supplements to follow-on applications. Currently, an applicant that submits an amendment to a pending 505(b)(2) application or supplement, or to a pending ANDA or supplement, is required to amend its patent certification if, at any time before approval, the applicant learns that the previously submitted patent certification is no longer accurate with respect to the pending application or supplement, as amended.[37] Under the proposed rule, a follow-on applicant would have been required to submit a patent certification or recertification for an amendment to its application if the amendment seeks: "(1) [t]o add a new indication or other condition of use; (2) to add a new strength; (3) to make other than minor changes in product formulation; or (4) to change the physical form or crystalline structure of the active ingredient."[38] For a supplement, the proposed rule would have required the submission of a patent certification or recertification for only the first two

categories of changes.[39]

Despite multiple comments on this proposal, the FDA's final rule finalizes the provision concerning amendments to unapproved follow-on applications;[40] however, the final rule does not finalize the provision concerning supplements to approved follow-on applications.[41] Citing comments suggesting ways in which the proposed supplement provision might permit gamesmanship by follow-on applicants, the FDA states in the preamble to the final rule that the FDA is continuing to evaluate these comments and will, for the time being, continue to regulate directly from the statute and general patent certification requirements in requiring an appropriate patent certification or statement with a 505(b)(2) or ANDA supplement.[42]

Listed Drugs Identified as Relied Upon by 505(b)(2) Applicants

Also notable in the FDA's final rule are the provisions related to which listed drugs a 505(b)(2) applicant must identify as "relied upon" in the 505(b)(2) application and, thus, submit patent certifications or statements. The final rule clarifies that a 505(b)(2) applicant must identify a pharmaceutically equivalent drug product approved in an NDA as a listed drug "relied upon" in the 505(b)(2) application if the pharmaceutically equivalent drug product was approved before the date of submission of the original 505(b)(2) application.[43] However, if there is more than one drug product that meets this criteria, the 505(b)(2) applicant is only required to identify one such pharmaceutically equivalent drug product as a relied upon listed drug. The purpose of this provision, according to the FDA, is to help ensure that the 505(b)(2) pathway is not used to circumvent the statutory obligation that would have applied if the proposed product was submitted is an ANDA — namely, submission of a patent certification for a listed patent that corresponds to the protected aspects of the pharmaceutically equivalent listed drug. 44 FDA acknowledges, however, that this provision could have the effect of subjecting a 505(b)(2) applicant to patent infringement litigation after approval (for patents claiming products that the 505(b)(2) applicant opts not to identify as a "relied upon" listed drug), but rejects the suggestion that this should be cause to modify the rule. [45] Rather, FDA dismisses this possibility as "one of many circumstances in which the timing of submission of an application has certain statutory or regulatory implications."[46]

Moving Forward

The provisions of the final rule take effect on Dec. 5, 2016. Due to the significance that the regulatory changes may have for both NDA holders and follow-on applicants, it will be critical that stakeholders on both sides review the rule's provisions carefully over the next 60 days. Failure to comply with the rule after that date could have substantial consequences for application filing and approval, exclusivity eligibility and 30-month stay determinations. Industry stakeholders should consult counsel with any questions about the impact of the rule's provisions.

—By John R. Manthei, J. Benneville Haas, Morgan A. Rettig, and Amy E. Speros, Latham & Watkins LLP

John Manthei and Ben Haas are partners at Latham & Watkins, in Washington, D.C. Morgan Rettig and Amy Speros are associates at Latham & Watkins, also in Washington, D.C.

[1] Abbreviated New Drug Applications and 505(b)(2) Applications; final rule, 81 Fed. Reg. 69,580 (Oct. 6, 2016) (to be codified at
21 C.F.R. pts. 314, 320) [hereinafter "final rule"]

[2] Abbreviated New Drug Applications and 505(b)(2) Applications; Proposed Rule, 80 Fed. Reg. 6802

(Feb. 6, 2015) [hereinafter
"Proposed Rule"].

[3] 21 C.F.R. § 314.53(c)(2)(i)(O), (c)(2)(i)(Q).

[4] 21 C.F.R. § 314.53(b)(1).

[5] Proposed Rule at 6820.

[6] Id.

[7] See Purepac Pharm. Co. v. TorPharm Inc., 354 F.3d 877, 880 (D.C. Cir. 2004).

[8] Proposed Rule at 6820.

[9] Proposed Rule at 6820.

[10] Proposed 21 C.F.R. § 314.53(c)(2)(i)(O)(2), (c)(2)(ii)(P)(2).

[11] Proposed 21 C.F.R. § 314.53(b)(1), (c)(2)(i)(O)(2), (c)(2)(ii)(P)(2), (c)(2)(ii)(P)(3).

[12] Proposed Rule at 6820.

[13] Proposed 21 C.F.R. § 314.53(c)(2)(ii)(P)(3)

[14] final rule at 69,598-99.

[15] final rule at 69,602.

[16] Id.

[17] 21 C,F,R, § 314.53(c)(2)(ii)

[18] Proposed Rule at 6821, 6845.

[19] Id.

[20] final rule at 69,601.

[21] Id. at 69,614-15.

[22] Proposed Rule at 6827.

[23] Id. at 6828.

[24] final rule at 69,604.

[25] Id. at 69,605.

[26] Proposed 21 C.F.R. § 314.53(f)(1).

[27] Id.

[28] Proposed Rule at 6835-36.

[29] Id.

[30] Id.

[31] Id.

[32] final rule at 69,611.

[33] Id.

[34] Proposed Rule at 6804.

[35] final rule at 69,623.

[36] Id.

[37] 21 C.F.R. §§ 314.50(i)(6)(iii), 314.94(a)(12)(viii)(V).

[38] Proposed Rule at 6847.

[39] Id.

[40] final rule at 69,615-16.

[41] Id. at 69,617.

[42] Id.

[43] Id. at 69,620.

[44] Id. at 69,621.

[45] Id.

[46] Id.
