Know the Rules! FDA's New Regulations Change Responsibilities For ANDA Filers

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On October 6, 2016, nearly thirteen years after passage of the Medicare Modernization Act (MMA), FDA published a final rule in the Federal Register implementing amendments and revisions to title 21 of the Code of Federal Regulations (C.F.R.) to conform the regulations governing the Hatch-Waxman Act with requirements set forth in the MMA. The changes to various sections of 21 C.F.R. include several significant provisions that will affect ANDA and 505(b)(2) applicants when the regulations go into effect on December 5, 2016. Although many of the revisions simply codify long-standing FDA practices and recommendations, changes to several key regulations will alter the landscape of paragraph IV patent litigation and will need to be accounted for immediately by ANDA applicants and holders. We have provided a brief summary of these important changes below. The main take-aways are:

1. A paragraph IV notice letters must be sent no later than twenty days after the defined postmarked date of a "paragraph IV acknowledgment letter," with extensions for when the twenty-day period falls on a weekend or federal holiday, and additional provisions when the paragraph IV certification is made in an amendment or supplement;
2. Paragraph IV notice letters can be sent by FedEx (or other designated delivery service) without prior FDA permission;
3. Dates that paragraph IV notice letters were sent and received for calculating forty-five day period for filing suit now reported in a single amendment thirty days after the last receipt date by an NDA holder or patent owner;
4. Paragraph IV recertifications are required when there are amendments (i) to indications or conditions of use; (ii) adding new strengths; (iii) making more than minor product formulation changes; or (iv) changes to active physical form;
5. Paragraph IV recertifications do not result in 180-day exclusivity forfeiture;
6. "Written consent" from the NDA and/or patent holder is required for ANDA approval in the event of an ANDA litigation settlement; and
7. "Commercial marketing" for purposes of starting the 180-day exclusivity period is defined to include the sale by the ANDA applicant of either the ANDA product or an authorized generic product sold under the NDA for the reference listed drug.

When a Paragraph IV Notice Letter Must Be Sent

For many years, ANDA applicants determined the start of the twenty-day period for sending a paragraph IV notice letter based on the date the applicant received an "acceptance for filing letter" via the United States Postal Service (USPS). If the twentieth day fell on a weekend or federal holiday, there was no clear guidance from FDA about whether the period could be extended to the next business day. The amendments to the regulations now clarify both issues.

In amending the Definition section of 21 C.F.R. § 314.3, FDA has stated that it will no longer issue "acceptance for filing letters" and instead will be issuing "paragraph IV acknowledgement letters" in accordance with terminology used in the MMA and the Generic Drug User Fee Act (GDUFA). *See* 21 C.F.R. § 314.3.

The twenty-day period to send the notice letter "begins on the *day after the date of the postmark* on the paragraph IV acknowledgement letter. When the 20th day falls on Saturday, Sunday, or a Federal holiday, the 20th day *will be the next day that is not a Saturday, Sunday, or Federal holiday.*" 21 C.F.R. § 314.95(b) (emphasis added). The new regulations define "postmark" depending on the method of transmission, as either the date the letter was received by the USPS or designated delivery service or transmitted electronically. *See* 21 C.F.R. § 314.3.

The amendments to 21 C.F.R. § 314.95(d) also explain when a notice letter must be sent if a paragraph IV certification is submitted as part of an amendment or supplement to a previously submitted ANDA. If the ANDA applicant submits the amendment or supplement including the paragraph IV certification *after* the ANDA has received a paragraph IV acknowledgement letter or other acknowledgement of receipt issued for ANDAs that do not include a paragraph IV certification, the paragraph IV notice letter must be sent *on the date the amendment or supplement is submitted. See* 21 C.F.R. § 314.95(d)(1). If, however, the ANDA applicant submits

the amendment or supplement including the paragraph IV certification *before* the FDA issues a paragraph IV acknowledgement letter or other acknowledgement of receipt, the paragraph IV notice letter must be sent *within the twenty-day period that begins on the day after the postmark of the paragraph IV acknowledgment letter.* *See* 21 C.F.R. § 314.95(d)(2).

How a Paragraph IV Notice Letter Must Be Sent

The amendments to 21 C.F.R. § 314.95 also resolve the long-time bane of ANDA applicants regarding how to send the paragraph IV notice letter. Under the old regulations, an ANDA applicant was required to send a paragraph IV notice letter by certified or registered U.S. mail with a return receipt unless obtaining prior FDA permission to send in another manner. As of December 5, 2016, a paragraph IV notice letter may be sent by "registered or certified mail, return receipt requested, or by a *designated delivery service* as defined in paragraph (g) of this section." 21 C.F.R. § 314.95(a) (emphasis added). Paragraph (g) defines a "designated delivery service" to include any public service such as UPS, FedEx, and DHL that electronically records postage and delivery dates and provides overnight or two-day delivery service in the United States. *See id.* at § 314.95(g).

Documenting the Timely Sending and Receipt of a Paragraph IV Notice Letter

The new regulations streamline the process for notifying the FDA concerning the dates a paragraph IV notice letter was sent by the applicant and then received by the NDA and/or patent holders. These dates are necessary for calculating the forty-five day period for filing suit under the Hatch-Waxman Act and the accompanying starting date for the statutory thirty-month stay of approval. Former regulatory practice required the ANDA applicant to submit multiple amendments providing separate identification of the date the paragraph IV notice letters were sent and the date or dates that the letter was received by the various interested parties. A regulation set forth at 21 C.F.R. § 314.95(e) simplifies this process by requiring ANDA applicants to submit a single amendment no later than thirty days after the *last* NDA or patent holder received the paragraph IV notice letter. The single amendment must contain (i) a copy of a sales or tracking receipt from the USPS or designated delivery service; (ii) a dated printout of the entry for Reference Listed Drug (RLD) in FDA's Orange Book that includes the patent or patents subject to the paragraph IV certification; and (iii) a return receipt or a signature proof of delivery. *See* 21 C.F.R. § 314.95(e).

Amendments Requiring a Paragraph IV Certification or Recertification

Over the past few years, FDA has faced several disputes over (i) the types of ANDA amendments that require an applicant to issue a new paragraph IV certification against a patent that had not previously been certified against or recertify against a patent that was already subject to a paragraph IV certification; and (ii) the effect of recertification on an applicant's potential 180-day exclusivity. *See, e.g., Paddock Labs., Inc. v. Ethypharm, S.A.,* Civ. No. 09-3799, 2010 WL 149860 at *3 (D. N.J. Jan. 18, 2011) (noting recertification was required when FDA required applicant to submit a Major Amendment changing formulation).

When must a certification or recertification be filed?

Previously, the only guiding regulation regarding the circumstances for amending a paragraph IV certification was 21 U.S.C. § 314.94(a)(12)(viii)(C), which requires an ANDA applicant to amend a submitted paragraph IV certification if "at any time before the effective date of the approval of the application, the applicant learns that the submitted certification is no longer accurate."

FDA has now clarified that an applicant will need to submit a patent certification, recertification, or section (viii) statement in 21 C.F.R. § 314.96(d) for any amendment to: (i) add a new indication or other condition of use; (ii) add a new strength; (iii) make other than minor changes in product formulation; or (iv) change the physical form or crystalline structure of the active ingredient. In its comments, FDA noted that it considers "minor changes in product formulation" to be:

> if the new formulation in the amendment is qualitatively (Q1) the same as the previous formulation (*i.e.,* contains all of the same inactive ingredients) and quantitatively (Q2) essentially the same (*i.e.,* each inactive ingredient differs by no more than plus or minus 5 percent from the previous formulation).

81 FR 69615 (Oct. 6, 2016).

Does recertification trigger forfeiture of 180-day exclusivity?

FDA also provided its position on whether a recertification against a patent that had already been subject to a paragraph IV certification based on 21 C.F.R. § 314.96(d)(1) would constitute a forfeiture of a first applicant's 180-day exclusivity in the Federal Register comments. In Response 42 printed in the Federal Register, FDA confirmed its position that a *recertification* required under 21 C.F.R. § 314.96(d) *would not constitute a forfeiture* of 180-day exclusivity. *See* 81 FR 69617-18 (Oct. 6, 2016).

Approval of ANDAs After a Litigation Settlement

FDA has now codified its position on the process by which an ANDA may be approved pursuant to a waiver or license after settlement of a patent litigation. In the event that an ANDA applicant settles a patent litigation by obtaining a waiver or license to exclusivity or patent rights possessed by the NDA holder, patentee, or their exclusive licensee(s), the ANDA may be approved on the waiver or

license date if the ANDA applicant submits "written consent" obtained from the patent and/or NDA holder for that approval. *See* 21 C.F.R. § 314.107(b)(3)(vi). FDA describes acceptable "written consent" as "[a] letter to FDA from the patent owner(s) or exclusive patent licensee that provides consent to approval of the 505(b)(2) application or ANDA any time on or after the date of consent," which may be submitted to FDA either alone or in combination with any actual settlement and/or license agreement. 81 FR 69629 (Oct. 6, 2016).

"Written consent" must be provided to FDA together with copies of any judgment, consent decree, or settlement order signed and entered by the court terminating the patent litigation, any order terminating the statutory stay of approval, and any order specifying that the ANDA may be approved no earlier than a specified date "*within 14 days* of the date of entry by the court…or the date of written consent to approval, as applicable." 21 C.F.R. § 314.107(e)(2) (emphasis added).

Definition and Notice of Commercial Marketing

To facilitate the approval of subsequent ANDAs, FDA has promulgated a definition for "commercial marketing" and a notice requirement designed to accelerate the date that a first applicant's 180-day exclusivity expires in certain circumstances. Under the Hatch-Waxman Act as amended by the MMA, a first applicant's 180-day exclusivity period begins to run on the first date of commercial marketing. *See* 21 U.S.C. 355(j)(5)(B)(iv)(I). FDA's new regulations define "commercial marketing" as follows:

> *Commercial marketing* is the introduction or delivery for introduction into interstate commerce of a drug product described in an ANDA, outside the control of the ANDA applicant, except that the term does not include transfer of the drug product for investigational use under part 312 of this chapter or transfer of the drug product to parties identified in the ANDA for reasons other than sale. Commercial marketing includes the introduction or delivery for introduction into interstate commerce of the reference listed drug by the ANDA applicant.

21 C.F.R. § 314.3. In other words, commercial marketing by any ANDA holder, including a first applicant, would include the sale by that ANDA holder of the approved ANDA product or an authorized generic product sold under the NDA for the RLD.

FDA has also created a requirement that a first applicant "must submit correspondence to its ANDA notifying FDA within 30 days of the date of its first commercial marketing of its drug product or the reference listed drug." 21 C.F.R. § 314.107(c)(2). If an applicant fails to notify FDA within the thirty-day period, the applicant risks a penalty: the FDA will deem the date of first commercial marketing "to be the date of the drug product's approval." *Id.* Thus, failure to notify the FDA within the set timeframe could potentially result in a forfeiture of some or all of an applicant's 180-day exclusivity period.

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FDA's new regulations place additional responsibilities on ANDA applicants in exchange for greater clarity about FDA's regulatory policies governing paragraph IV certifications, 180-day exclusivity, and ANDA approval requirements. ANDA applicants must be mindful of these new requirements to ensure that none of their rights are jeopardized.

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