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Ten Takeaways From the FDA's December 2016 Revisions to its Hatch-Waxman Regulations



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Drug manufacturers need to be aware of new significant changes to the regulations governing the approvals of New Drug Applications, 505(b)(2)s, and Abbreviated New Drug Applications and their impact on pending or future Hatch-Waxman litigations. On October 6, 2016, the Food and Drug Administration ("FDA") published a Final Rule titled "Abbreviated New Drug Applications and 505(b)(2) Applications" revising its regulations to implement certain provisions of the Medicare Modernization Act of 2003 ("MMA"). (81 Fed. Reg. 69,580 (codified at 21 C.F.R. pt. 314)). The new regulations went into effect on December 5, 2016. While some revisions codified existing FDA practices, other revisions related to 505(b)(2) and ANDAs reflected changes in case law over the past decade and facilitated compliance with the Hatch-Waxman statute. (*Id.* at 69,580). In publishing its Final Rule, the FDA also considered the comments it received on its Proposed Rule published on February 6, 2015. (80 Fed. Reg. 6802 (Feb. 6, 2015)).

The new regulations have major implications for NDA holders, 505(b)(2) applicants, and ANDA filers. This article highlights 10 critical takeaways, but companies with existing and future submissions to the FDA should consult counsel to adjust their applications and litigation strategies accordingly.

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1. The new regulations will apply to new and existing submissions.

The new regulations apply not only to new NDAs, 505(b)(2) applications, and ANDAs submitted after December 5, 2016, but also to existing submissions in certain situations. According to the FDA, the new regulations apply to new submissions and amendments or supplements to existing submissions (including patent certifications or statements). (81 Fed. Reg. at 69,632). The new regulations also apply to existing submissions when a party receives a court decision that affects approval of its pending submission. (*Id.*). Further, where an NDA holder submits or revises patent information or a third party initiates a patent listing dispute to confirm accuracy and relevancy of patent information in the Orange Book, the new regulations would apply to the af-

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fected submission as well. (*Id.*). Thus, a number of existing submissions without approval will be affected by the new regulations.

2. NDA holders need to provide specific use codes for their drugs.

For NDA holders, perhaps the new regulations' most significant change is the requirement that they address what FDA terms ''overbroad and ambiguous'' use codes that may delay generic applications. The new regulations require an NDA holder to provide a use code for its branded drug that describes only the specific method of use claimed by the patent listed in the Orange Book for the drug. (Revised 21 C.F.R. § 314.53(b)(1)). Further, for approved NDAs, the NDA holder must ''identify with specificity the section(s) and subsection(s) of the approved labeling that describes the method(s) of use claimed by the patent submitted.'' (Revised 21 C.F.R. §§ 314.53(b)(1), (c)(2)). In other words, NDA holders need to be aware that the scope of a use code must be limited to the scope of the patent claim, must describe a patented method of use approved by the FDA, and must be reflected in the approved product labeling. (Revised 21 C.F.R. § 314.53(b)(1)).

The FDA provided three ''general principles'' for the content of use codes: where the patented method of use is (1) broader than the approved indication (''the use code would need to be phrased more narrowly than the patent claim to only describe the specific patented method-of-use that is described in FDA-approved product labeling''); (2) coextensive with the approved indication (''the use code must describe only the specific approved method of use claimed by the patent''); and (3) narrower than the approved indication (the use code ''must describe only the specific approved method of use claimed by the patent''). (81 Fed. Reg. 69,598-99).

The new regulations should give 505(b)(2) and ANDA applicants greater certainty as to the indications they can seek approval for without infringing on a method-of-use patent and the language that should be carved out from their drug labels to avoid a charge of infringement on the claimed use. According to the FDA, that is the purpose of the revised regulations: to require NDA holders to provide adequate information about the scope of listed method-of-use patents such that 505(b)(2) and ANDA applicants can assess whether a listed patent claims a use for which the 505(b)(2) or ANDA applicant is not seeking approval. (81 Fed. Reg. at 69,581). These changes will assist the FDA in evaluating whether a generic's section viii statement and proposed labeling carve-out is appropriate. (*Id.*).

3. Third parties can dispute the accuracy or relevance of patent information in the Orange Book.

With the new regulations, FDA created a new mechanism for third parties to dispute the accuracy or relevance of patent information in the Orange Book. This dispute mechanism may prove key for generic applicants in challenging patents listed in the Orange Book, but that the applicant believes do not cover the approved brand product.

Under the new regulations, a third party can submit a written request to the FDA with ''a statement of dispute that describes the specific grounds for disagreement regarding the accuracy or relevance of patent information.'' (Revised 21 C.F.R. § 314.53(f)(1)). 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 confirm the correctness of the patent information or withdraw or amend the patent information. (*Id.*). If the patent holder timely responds, the FDA will retain or amend the patent information in the Orange Book in accordance with the response. (*Id.*). This dispute mechanism applies to drug product, drug substance, and method-of-use patents. (*Id.*).

Further, to keep the public informed, the new regulations state that the FDA will ''promptly'' post information on its Web site regarding whether a patent listing dispute has been submitted for a published description of a patented method-of-use for a drug product and whether the NDA holder has timely responded to the patent listing dispute. (Revised 21 C.F.R. § 314.53 (f)(1)(iii)).

4. NDA holders must update the Orange Book listing in certain circumstances.

NDA holders should be aware of the new obligations FDA has imposed on them to keep the Orange Book updated. If an NDA holder determines that a patent no longer meets the requirements for listing (including if there has been a judicial finding of invalidity for a listed patent, from which no appeal has been or can be taken), the NDA holder is required to ''promptly'' notify the FDA to amend the patent information or withdraw the patent or patent information and request that the patent or patent information be removed from the list. (Revised 21 C.F.R. § 314.53(f)(2)(i)). The FDA noted that it would consider withdrawal or amendment of the patent information to be timely if done ''within 14 days of the date on which the NDA holder determines that the patent or patent claim no longer meets the requirements of the listing'' (81 Fed. Reg. 69,607). But the FDA declined to consider a patent untimely filed if the NDA failed to notify the FDA within that 14 day period. (*Id.*) The FDA noted that courts can enforce a failure to comply with an order; therefore generic filers should, when asking for relief on the basis invalidity from a court, request an order from the judge that the NDA holder delist the patent. (*Id.*).

5. FDA will not delist from the Orange Book a patent that is the basis of a generic applicant's 180-day marketing exclusivity.

First applicants with 180-day exclusivities should take heart—they cannot lose their first-filer status even if an NDA holder requests delisting of the patent from the Orange Book. The new regulations codify the FDA's long-standing practice of not removing a patent from the Orange Book list if a generic applicant is eligible for 180-day exclusivity based on that patent, even if an NDA holder requests removal of a patent or patent information from the list. (Revised 21 C.F.R. §§ 314.50(i)(6)(ii), 314.94(a)(12)(viii)(B)).

Notably, the new regulations do not address other circumstances under which an ANDA applicant may be

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deemed to have forfeited 180-day exclusivity. In commentary to the Final Rule, the FDA instead stated that it will continue to implement those provisions of the MMA directly from the statute, and may later issue a separate rule. (81 Fed. Reg. at 69,628).

6. First applicants with 180-day exclusivities now have a marketing notice requirement.

First applicants with 180-day exclusivities should be aware that the new regulations introduce a marketing notice requirement for a first applicant, and impose a severe penalty for non-compliance. A first applicant is required to notify FDA within 30 days of the date of the first ''commercial marketing'' of its drug. (Revised 21 C.F.R. § 314.107(c)(2)). If the first applicant fails to do so, the date of the ANDA's approval is deemed to be the date of first commercial marketing. (*Id.*). Thus, failure to notify the FDA in the 30-day timeframe could result in loss of some of the first applicant's 180-day exclusivity period.

The new regulations also define ''commercial marketing'' as the ''introduction or delivery for introduction into interstate commerce of a drug product described in an approved ANDA, *outside the control of the ANDA holder*.'' (Revised 21 C.F.R. § 314.3) (emphasis added)). The FDA clarified that ''commercial marketing'' does not include the ANDA applicant's shipment of its ANDA drug product to parties identified in the ANDA for reasons other than sales, for example, packagers, repackagers or storage or distribution facilities.(81 Fed. Reg. at 69,592).

7. The regulations codify the availability of the 30-month stay for different litigation scenarios.

All drug companies anticipating or currently involved in Hatch-Waxman litigations should understand the new regulations' revisions to the 30-month stay (or 7 1/2 years where applicable) for different litigation scenarios.

The FDA's new regulations addressing 30-month stays and preliminary injunctions are meant to encourage NDA holders to move for a preliminary injunction well in advance of the expiration of the 30-month stay. If a preliminary injunction is entered before the expiration of a 30-month stay, the FDA will extend the stay until the court decides issues of patent infringement and validity. (Revised 21 C.F.R. § 314.107(b)(3)(v)). The FDA declined to establish a regulation addressing the timing of approval of a 505(b)(2) and ANDA if the district court were to enter a preliminary injunction after the expiration of the 30-month stay, but suggested that, to ensure the ANDA is not approved, NDA holders ask for an injunction order that specifies the scope and duration of the injunction. (81 Fed. Reg. at 69,626). If a court order requires termination of the 30-month stay, the application may be approved. (*Id.* at 69,627).

The FDA also noted that a voluntary agreement not to market or provide pre-launch notice will not have the same effect as a preliminary injunction, and will not require a stay beyond the 30 months. (*Id.* at 69,626). The FDA may also approve an application notwithstanding an agreement between the NDA holder and applicant—allowing the applicant to choose not to make or sell the product until the agreed upon date. (81 Fed. Reg. at 69,627). This rule may give NDA holders a reason to pursue a preliminary injunction, but a potential resolution might be addressed in the private agreement between the parties. And, if an agreement consenting to approval is reached, the 30-month stay is terminated, and approval may be granted on or after the date of consent. (Revised 21 C.F.R. § 314.107(b)(3)(vi)).

Further, the FDA clarified that if a court enters an order of dismissal without finding infringement in each pending suit brought within the 45 days of receipt of the notice of paragraph IV certification, a corresponding 30-month stay will be terminated. (Revised 21 C.F.R. § 314.107(b)(3)(viii)).

8. NDA holders have additional responsibilities so that their patents are not considered late-listed.

Late-listed patents, or patents not listed within a specified timeframe in the Orange Book, have particular implications for generic drug companies—applicants with pending ANDAs and 505(b)(2) applications need not certify to a late-listed patent. (*Id.*). Without such a certification, the NDA holder cannot avail of the statutory 30-month stay that it would otherwise be entitled to if it were to sue the generic company within 45 days of receiving such notice. (21 U.S.C. § 355(c)(2012)).

FDA regulations have always required NDA holders seeking to timely list a patent to submit patent information to the Orange Book within 30 days of approval of the NDA, and for patents issued after the date of approval of the NDA, within 30 days of issuance of the patent. (21 C.F.R. § 314.53(c)(2)(ii) (Apr. 2016)). Under the new regulations, NDA holders must meet an additional obligation to avoid their method-of-use patents from being late-listed: NDA holders are required to submit an ''amendment to the description of the approved method(s) of use claimed by the patent [] within 30 days of a decision by the USPTO, or by a Federal district court, the Court of Appeals for the Federal Circuit, or the U.S. Supreme Court that is specific to the patent and alters the construction of a method-of-use claim(s) of the patent.'' (Revised 21 C.F.R. §§ 314.50(i)(4)(i), 314.94(a)(12)(vi)(A)(3)). Significantly, a pre-judgment claim construction decision may be sufficient to trigger the NDA holder's obligation to submit an amendment; in commentary to the Final Rule, the FDA specified that revisions to the use code could be ''based on a patent-specific decision by the USPTO. . .or by a Federal court (e.g., Markman hearing) that construes the terms of the patent claim(s).'' (81 Fed. Reg. 69602).

Notably, generic companies will no longer have to resort to non-FDA sources to determine whether a patent was late-listed in the Orange Book. In commentary to the Final Rule, the FDA stated it intends to list the date of submission of patents and patent information in the Orange book ''on a prospective basis beginning as soon as practicable after the effective date of the rule.'' (81 Fed. Reg. at 69,603).

9. ANDA or 502(b)(2) applicants have heightened certification requirements.

Generic applicants now have guidance on the types of amendments that require a certification or recertification. The guidance is important for generic companies because these certifications could trigger a first or second 30-month stay of approval in certain cases. (*Id.* at 69,616). The new regulations specify that an ANDA applicant has to amend its ANDA with an appropriate patent certification or recertification if a certification had already been submitted for one of the following reasons: 1) to add a new indication or other condition of use; 2) to add a new strength; 3) to make other than minor changes in the product formulation; and 4) to change the physical form or crystalline structure of the active ingredient. (Revised 21 C.F.R. §§ 314.60(f), 314.96(d)).

10. Reissued Patents are distinct from the original patent for certification purposes.

The FDA will now consider ''reissued patents as separate and distinct from the original patent for purposes of administering the patent certification requirements . . . and any 30-month stay of approval or 180-day exclusivity.'' (81 Fed. Reg. at 69,601). If a patent is reissued, the NDA holder must withdrawal the original patent and submit an amendment or supplement to the NDA. (*Id.*; revised 21 C.F.R. § 314.53(f)(2)).

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According to the FDA, the purpose of the revised regulations is to ''reduce unnecessary litigation, reduce delays in the approval of 505(b)(2) applications and ANDAs, and provide business certainty to both brand name and generic drug manufacturers.'' (81 Fed. Reg. at 69,580). Updated rules were long overdue, and implementation of the new rules will impact both brand and generics' short and long term strategies.

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