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June 8, 2015

Division of Dockets Management (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, Room 1061  
Rockville, MD 20852

**Re: Docket No. FDA-2011-N-0830: Abbreviated New Drug Applications and 505(b)(2) Applications; Proposed Rule, 80 Fed. Reg. 6802 (Feb. 6, 2015)**

Dear Sir or Madam:

The Pharmaceutical Research and Manufacturers of America (PhRMA) is pleased to provide comments on the Food and Drug Administration's (FDA's) proposed rule entitled "Abbreviated New Drug Applications and 505(b)(2) Applications," which would implement the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA).<sup>1</sup> PhRMA represents the country's leading innovative biopharmaceutical research companies, which are devoted to discovering and developing medicines that enable patients to live longer, healthier, and more productive lives. PhRMA companies are leading the way in the search for new cures, with members investing an estimated \$51 billion in 2014 in the discovery and development of new medicines.

PhRMA applauds FDA's publication of the proposed rule and the agency's work to implement the MMA. We actively participated in the 2004 comment process regarding regulatory actions necessary for implementation and appreciate FDA's consideration of those comments.<sup>2</sup> In particular, PhRMA appreciates the agency's adoption of some of our prior suggestions—such as developing regulations that clarify the timeframe during which notice of a paragraph IV certification must be given and that impose an administrative consequence for noncompliance, thereby providing a mechanism for limiting serial paragraph IV notices. We also support other provisions included in the proposed rule, including provisions that:

- Streamline requirements for listing drug product and substance claims in *Approved Drug Products With Therapeutic Equivalence Evaluations* (the Orange Book);
- Provide clarity for Orange Book listing of polymorph patents; and

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<sup>1</sup> 80 Fed. Reg. 6802 (Feb. 6, 2015).

<sup>2</sup> See PhRMA, Comments on Docket No. 2004N-0087 (May 3, 2004), at 1.

- Institute less repetitive Orange Book listing obligations for supplements to new drug applications (NDAs).

We offer our specific comments below, including several suggestions and requests for clarification. Of particular note, we recommend that FDA clarify how NDA holders and patent owners should set use codes and that FDA refrain from deferring to a 505(b)(2) or abbreviated new drug application (ANDA) applicant's interpretation of a listed patent's scope in the event of a use code dispute, particularly where the NDA holder has confirmed the use code's correctness. We also urge FDA to take this opportunity to clarify its stance on the listability of patents covering device constituents of NDA-approved drug-device combination products. PhRMA further recommends that FDA revise the proposed regulations to confirm that the agency will not approve a pending 505(b)(2) application or ANDA if a district court finds patent infringement after a 30-month stay or 7<sup>1</sup>/<sub>2</sub>-year period has expired. We also ask FDA to make explicit in its final regulations that the issuance of a preliminary injunction after expiry of the 30-month or 7<sup>1</sup>/<sub>2</sub>-year period stays approval through at least the appeal, if the district court finds patent infringement.

## **I. Patent Listing and Related Topics**

### **A. Use Codes**

PhRMA recommends that FDA clarify its proposals regarding use codes in several respects to better achieve the agency's stated goals of "reduc[ing] unnecessary litigation, reduc[ing] delays in the approval of 505(b)(2) applications and ANDAs that are otherwise ready to be approved, and provid[ing] business certainty to both brand name and generic drug manufacturers."<sup>3</sup> As described further below, we recommend changes to the proposals on the content of use codes, to ensure consistency with FDA's past statements that a use code should not substitute for an applicant's substantive review of the underlying patent and approved labeling. We also urge FDA to reconsider its proposals to deem certain use code changes as untimely filed and to defer to an applicant's interpretation of patent scope in use code disputes.

#### *1. Content and Submission*

PhRMA recommends that FDA further delineate its expectations for the content of use codes, describe how it will employ these use codes in determining whether applicants' proposed labeling properly omits protected information, and re-evaluate its proposal to regard certain use code changes as late-filed.

In the preamble to the proposed rule, FDA states that, in an effort to "restrain overbroad use codes" that "may delay approval of generic drugs," it is proposing to clarify the requirements

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<sup>3</sup> 80 Fed. Reg. at 6803.

for the description of the patented method of use.<sup>4</sup> Specifically, FDA proposes to “codify [its] longstanding requirement” 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) or ANDA applicant is not seeking approval; for example, if the scope of the method-of-use claim(s) of the patent does not cover every approved use of the drug, then the description of the patented method of use must contain only the specific portion(s) of the indication or other method of use claimed by the patent[.]<sup>5</sup>

There is tension between this proposal and FDA’s statements regarding the purpose of a use code, including one quoted in this preamble. FDA has explained that “[u]se codes are intended to alert ANDA and 505(b)(2) applicants to the existence of a patent that claims an approved use. *They are not meant to substitute for the applicant’s review of the patent and the approved labeling.*”<sup>6</sup> The proposed rule however, appears to disregard this approach to the setting of use codes. Indeed, under the proposed rule, a use code must facilitate the applicant’s substantive review of the patent; the use code must “provide adequate information. . . . to enable potential 505(b)(2) and ANDA applicants to avail themselves of the statutory provision that permits a 505(b)(2) or ANDA applicant to not certify to a patent by [submitting a section (viii) statement] and carving out from product labeling the corresponding use information.”<sup>7</sup>

PhRMA believes that this proposal is unrealistic and unworkable, given that use codes cannot exceed 240 characters. FDA has recognized that “in some cases 240 characters may not fully describe the use as claimed in the patent.”<sup>8</sup> For example, if a patent contains a series of claims of varying scope, the nuances of the various claims may not be captured in 240 characters. In fact, given that the U.S. Patent and Trademark Office has reviewed and allowed a patent to issue with certain claim language, we believe that it is inappropriate to suggest that the use code system—created as a matter of administrative convenience—should usurp the responsibility of applicants in ascertaining the scope of a patent from actually looking to the patent claims. FDA’s proposed approach imports speculation and imprecision into the process of setting use codes, as it would require the NDA or patent holder to guess what future ANDA and

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<sup>4</sup> *Id.*

<sup>5</sup> *Id.* at 6884 (proposed 21 C.F.R. § 314.53(c)(2)(ii)(P)(3)).

<sup>6</sup> *Id.* at 6828 (quoting Applications for FDA Approval to Market a New Drug: Patent Submission and Listing Requirements and Application of 30-Month Stays on Approval of Abbreviated New Drug Applications Certifying That a Patent Claiming a Drug is Invalid or Will Not Be Infringed, Final Rule, 68 Fed. Reg. 36676, 36683 (June 18, 2003)) (emphasis added).

<sup>7</sup> *Id.* at 6827.

<sup>8</sup> 68 Fed. Reg. at 36683.

505(b)(2) applicants would seek to carve out of the labeling for their proposed products in view of the patent claims.

Moreover, NDA holders lack sufficient guidance as to the level of detail required when identifying specific sections of the approved labeling that support a listing. We suggest that FDA clarify the manner in which NDA holders are to identify on Form FDA 3542 or Form FDA 3542a the specific sections of drug labeling that correspond to the specific portion(s) of the indication or other condition of use claimed by the patent. NDA holders also lack sufficient guidance as to how to set a use code that FDA will deem adequate. FDA has to date provided minimal guidance on the appropriate substance of use codes.

We believe it would be helpful if FDA could provide hypothetical examples that demonstrate how an NDA or patent holder should set a use code if the patented method-of-use claim is broader, narrower, or co-extensive with approved indications or conditions of use for a drug. Similarly, we recommend that FDA provide guidance—including hypothetical examples—that explains how to set a use code when the patent and the approved labeling use different terminology. Further, we recommend that FDA provide advice on setting use codes when the implicated portions of the labeling appear outside the indications statement. We believe that robust agency guidance regarding use codes would provide NDA holders with much needed clarity about setting use codes and, thus, address FDA's concerns about "overbroad" use codes.<sup>9</sup> We also believe this approach is fairer and more appropriate than the proposal to defer to the applicant's interpretation of the scope of a patent, as discussed further below.

Relatedly, PhRMA recommends that FDA explain how it applies a use code to make decisions regarding a 505(b)(2) or ANDA applicant's proposed carve-out of a protected condition of use. A detailed description of FDA's approach to assessing carve-outs would assist NDA holders in setting use codes that are more helpful to FDA in the first instance and allow the agency to more easily and efficiently implement the provisions of the Federal Food, Drug, and Cosmetic Act (FDCA) that permit applicants to declare they are not seeking approval for a patented use and carve out from the product labeling the corresponding use information.<sup>10</sup>

Given the continued uncertainty surrounding how to set use codes, PhRMA encourages FDA to reconsider its proposal to treat certain changes to use codes as untimely filed. While FDA characterizes the proposed rule as a codification of the agency's longstanding use code practice, ambiguity and considerable confusion has surrounded the setting of use codes for years;

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<sup>9</sup> Relatedly, we note that question 4.2b on Form 3542 directs the NDA holder to "submit the description of the approved indication or method of use" for inclusion as the use code in the Orange Book. This alternative directive is potentially confusing as it suggests submitting language from either the approved labeling or the patent claims. See also 21 C.F.R. §§ 314.53(c)(2)(P)(1) and (3); 21 C.F.R. § 314.53(e); *Caraco Pharm. Labs., Ltd. v. Novo Nordisk A/S*, 132 S. Ct. 1670, 1683, n.7 (2012). We encourage FDA to state more clearly the information required for publication.

<sup>10</sup> See FDCA §§ 505(b)(2)(B) and 505(j)(2)(C)(viii).

and, as noted, clarity in this space is still lacking. The proposed rule expands the category of untimely filed patent information to include an NDA holder's amendment to the use code if "[t]he amendment is submitted more than 30 days after patent issuance and it is not related to a corresponding change in approved product labeling"; or "[t]he amendment is submitted more than 30 days after a corresponding change in approved product labeling."<sup>11</sup> There are significant ramifications that accompany an untimeliness designation (i.e., a 505(b)(2) or ANDA applicant with a pending application would not be required to certify to the patent), and we urge FDA to refrain from imposing such a drastic consequence in such an unsettled area of patent listing practice. Indeed, FDA's proposed approach would act as a penalty on NDA and patent holders and discourage the very result that FDA seeks: the setting of accurate use codes.

## 2. *Dispute Resolution Process*

PhRMA urges FDA to clarify its proposed "enhance[d]"<sup>12</sup> mechanism for resolving use code disputes and reconsider its proposal to accord deference to the applicant's interpretation of the scope of a patent in certain circumstances. Under the proposed rule, if any person challenges the accuracy or relevance of a use code published in the Orange Book, that person must notify FDA in writing and state the grounds for disputing the patent listing.<sup>13</sup> FDA would then ask the NDA holder to confirm that the use code is correct; within 30 days of FDA's request, an NDA holder must confirm the correctness of the use code and provide information on the specific approved use claimed by the patent to enable FDA to make a carve-out determination.<sup>14</sup> The proposed rule provides:

If there is insufficient information to make a [carve-out determination], and the NDA holder has confirmed the correctness of its description of the specific approved use claimed by the patent, the Agency will review the proposed labeling for the 505(b)(2) application or ANDA with deference to the 505(b)(2) or ANDA applicant's interpretation of the scope of the patent.<sup>15</sup>

First, given inconsistencies between the text of the proposed rule and the corresponding preamble discussion, it is unclear when the agency proposes to defer to an applicant's interpretation of the scope of the patent. In the preamble, FDA states that deference will be afforded to the applicant's interpretation in three scenarios:

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<sup>11</sup> 80 Fed. Reg. at 6880 (proposed 21 C.F.R. § 314.50(i)(4)) and 6888 (proposed 21 C.F.R. § 314.94(a)(12)(vi)).

<sup>12</sup> *Id.* at 6827.

<sup>13</sup> *Id.* at 6885 (proposed 21 C.F.R. § 314.53(f)(1)).

<sup>14</sup> *Id.*

<sup>15</sup> *Id.*

If the patent has been listed and the NDA holder confirms the accuracy of the patent information, fails to timely respond to FDA's request under § 314.53(f), or submits a revision to the use code that does not provide adequate clarity for FDA to determine whether the scope of the proposed labeling carve-out would be appropriate based on the NDA holder's use code and approved labeling[.]<sup>16</sup>

The proposed rule, however, includes different language as quoted above and does not appear to contemplate deference in each of these scenarios (e.g., when the NDA holder's response is untimely). Accordingly, we recommend that FDA clarify the circumstances under which the agency plans to defer to an applicant's interpretation of the patent's scope.

Additionally, given ambiguities in the proposed rule, it is unclear whether an NDA holder who responds to a use code challenge by clarifying or amending the use code would be viewed as submitting an untimely change. We recommend that FDA revise proposed sections 314.50(i)(4)<sup>17</sup> and 314.94(a)(12)(vi)<sup>18</sup> to state more clearly that amendments submitted in response to a use code dispute pursuant to section 314.53(f)(1)<sup>19</sup> will not be considered untimely filed. We also urge FDA to provide explicitly that, when an NDA holder submits supplementary information to FDA to clarify its interpretation—such as information supporting the NDA holder's position that the original use code was correct or “information on the specific approved use claimed by the patent that enables the Agency to make a [carve-out] determination”<sup>20</sup>—this

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<sup>16</sup> *Id.* at 6827; *see also id.* at 6804.

<sup>17</sup> The proposed rule states in relevant part: “Except as provided in § 314.53(f)(1), an NDA holder's amendment to the description of the approved method(s) of use claimed by the patent will be considered untimely filing of patent information if: (i) The amendment is submitted more than 30 days after patent issuance and it is not related to a corresponding change in approved product labeling; or (ii) The amendment is submitted more than 30 days after a corresponding change in approved product labeling.” *Id.* at 6880 (proposed 21 C.F.R. § 314.50(i)(4)).

<sup>18</sup> The proposed rule states in relevant part: “Except as provided in § 314.53(f)(1), an NDA holder's amendment to the description of the approved method(s) of use claimed by the patent will be considered untimely filing of patent information if: (A) The amendment is submitted more than 30 days after patent issuance and it is not related to a corresponding change in approved product labeling; (B) The amendment is submitted more than 30 days after a corresponding change in approved product labeling.” *Id.* at 6888 (proposed 21 C.F.R. § 314.94(a)(12)(vi)).

<sup>19</sup> The proposed rule states that, in the case of a use code dispute: “FDA will request that the NDA holder confirm the correctness of its [use code] . . . Unless the NDA holder withdraws or amends its patent information in response to FDA's request, the Agency will not change the patent information in the list. . . . However, if there is insufficient information to make a determination in accordance with section 505(b)(2)(B) or 505(j)(2)(C)(viii) of the Federal Food, Drug, and Cosmetic Act, and the NDA holder has confirmed the correctness of its description of the specific approved use claimed by the patent, the Agency will review the proposed labeling for the 505(b)(2) application or ANDA with deference to the 505(b)(2) or ANDA applicant's interpretation of the scope of the patent.” *Id.* at 6885 (proposed 21 C.F.R. § 314.53(f)(1)).

<sup>20</sup> *Id.*

submission of information does not amount to an untimely amendment, even if it changes FDA's view regarding the meaning of the use code. Without these clarifications, 505(b)(2) and ANDA applicants may be under the misimpression that the NDA holder's clarification of the use code pursuant to section 314.53(f)(1) absolves the applicants of the obligation to submit a paragraph IV certification in more circumstances than FDA seems to intend.

PhRMA further recommends that FDA abandon its proposal to defer to the 505(b)(2) or ANDA applicant's interpretation of the scope of a patent when disputes arise. A more measured approach to disagreements about the accuracy and relevance of use codes is appropriate given the lack of substantive guidance on setting use codes in the first instance and the fact that FDA's approach could be highly prejudicial to an NDA holder's patent rights. Moreover, a measured approach is more consistent with FDA's intent that its role with respect to patent listing remain "ministerial";<sup>21</sup> assessment of the adequacy of use codes and legally significant nuances in patent claims to determine whether such deference is warranted requires patent expertise and resources that FDA does not have.<sup>22</sup> A measured approach also is more consistent with FDA's longstanding view, discussed above, that use codes are not meant to substitute for full review of the underlying patents. Deference is particularly inappropriate where the NDA holder has confirmed that the use code has been correct all along. If FDA defers to the applicant's interpretation of the patent's scope even in these circumstances, 505(b)(2) and ANDA applicants will be incentivized to dispute nearly every method-of-use patent listing so as to achieve this deference.

Furthermore, the proposed dispute resolution procedure and FDA's current plan to accord deference to the applicant's patent scope interpretation could enable 505(b)(2) or ANDA applicants to avoid submitting a paragraph IV certification in favor of a section viii statement by challenging the use code and advancing a narrow interpretation of the patent claim(s). This would allow the applicant to avoid the requirement to notify the NDA holder of its application and thus the possibility of a 30-month stay that should otherwise be available to the NDA holder under the FDCA. FDA has expressed a desire to avoid this sort of circumvention of statutory obligations in other contexts, and we encourage FDA to take a similar approach with respect to use codes.<sup>23</sup>

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<sup>21</sup> See, e.g., *id.* at 6828 ("As previously discussed in the June 2003 final rule, we reiterate that the Agency's role in patent listing is ministerial and does not involve substantive review of patents.") (citation omitted).

<sup>22</sup> See *id.* at 6846 (in the context of amended patent certifications upon patent reissuance and the effect on the availability of 30-month stays, opting to treat the original and reissued patent as a "single bundle" of rights and explaining, "[i]f FDA were to propose a different approach to the availability of a 30-month stay based on a paragraph IV certification to a *reissued patent with broadened claims*, the implementation of such an approach would require resources and patent expertise that FDA currently does not possess and would be inconsistent with the Agency's ministerial role in patent listing.") (emphasis added).

<sup>23</sup> See *id.* at 6856 (discussing proposed revision to 21 C.F.R. § 314.54(a)(1)(iii) and explaining the requirement is "intended to help ensure that the 505(b)(2) pathway is not used to circumvent the statutory obligation that would (continued...)

B. Listing of Patents Covering Devices in Drug-Device Combination Products

PhRMA urges FDA to clarify its stance on the listability of patents covering device constituents of NDA-approved drug-device combination products in connection with this rulemaking. Since 2005, multiple manufacturers have asked FDA for advisory opinions on this topic,<sup>24</sup> but the agency has not substantively responded. The lingering uncertainty on this issue has since been the subject of litigation.<sup>25</sup> Thus, in connection with finalizing the proposed rule, FDA should confirm that these patents are listable in the Orange Book.

FDA regulations provide that applicants must list patents that claim “the drug or a method of using the drug that is the subject of the [NDA] or amendment or supplement to it and with respect to which a claim of patent infringement could reasonably be asserted . . . .”<sup>26</sup> These patents include drug product patents, as that term is defined in 21 C.F.R. § 314.3,<sup>27</sup> and FDA has recognized that drug delivery devices and their associated protective packaging (approved as part of an NDA) can be integral parts of the drug product.<sup>28</sup> Numerous manufacturers have alerted

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have applied if the proposed product was submitted as an ANDA—namely, submission of a patent certification for a listed patent”).

<sup>24</sup> See Novo Nordisk Inc., Request for Advisory Opinion, Docket No. FDA-2012-A-1169 (Nov. 26, 2012) [hereinafter, “Novo Nordisk Advisory Opinion Request”]; Finnegan, Henderson, Farabow, Garrett & Dunner, LLP on behalf of Forest Laboratories, Inc., Request for Advisory Opinion Regarding Patents Listable in the Orange Book in Connection with NDA No. 202-450, Docket No. FDA-2011-A-0363 (May 12, 2011) [hereinafter “Forest Labs. Advisory Opinion Request”]; Ropes & Gray LLP on behalf of AstraZeneca, Request for an Advisory Opinion -- “Orange Book” Listing of Patents, Docket No. 2007A-0261 (June 21, 2007) [hereinafter “Astra Zeneca Advisory Opinion Request 2007”]; Ropes & Gray LLP on behalf of AstraZeneca, Request for Advisory Opinion Concerning “Orange Book” Listing of Patents, Docket No. 2006A-0318 (Aug. 10, 2006) [hereinafter “Astra Zeneca Advisory Opinion Request 2006”]; GlaxoSmithKline, Request for Advisory Opinion Concerning “Orange Book” Listing of Patents, Docket No. 2005A-0015 (Jan. 10, 2005) [hereinafter “GSK Opinion Request”].

<sup>25</sup> See *King Pharms., Inc. v. Intelliject, Inc.*, No. 1:11-cv-00065-UNA (D. Del. Jan. 19, 2011) (generic applicant filed counterclaim seeking to delist information about a device-related patent from the Orange Book on the basis that the patent did not claim or disclose either a composition or a formulation of the active ingredient). Prior to a ruling on this issue, the litigation was dismissed pursuant to the parties’ settlement agreement.

<sup>26</sup> 21 C.F.R. § 314.53(b).

<sup>27</sup> FDA has said that metered aerosols, metered sprays, and pre-filled drug delivery systems are included within the definition of “drug product” under 21 C.F.R. § 314.3. 68 Fed. Reg. at 36680.

<sup>28</sup> See FDA, Draft Guidance for Industry: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action, at lines 208-11 (Apr. 2003) (“Nasal aerosols usually consist of the formulation, container, valve, actuator, dust cap, associated accessories, and protective packaging, *which together constitute the drug product*. Similarly, nasal sprays usually consists of the formulation, container, pump, actuator, protection cap, and protective packaging, *which together constitute the drug product*.”) (emphases added); FDA, Draft Guidance for Industry: Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products, at lines 1932-35 (Oct. 1998) (under “Glossary of Terms,” providing that “[f]or MDIs, the formulation, container, the valve, the actuator, and any associated accessories (e.g., spacers) or protective packaging collectively constitute the drug product” and “[f]or DPIs, the formulation, and the device with all of its parts including any protective packaging (e.g., overwrap) constitute the drug product”).



FDA to their practice of submitting these patents to FDA for listing, and FDA has both accepted these submissions and subsequently listed the patents in the Orange Book, strongly implying that the agency concurs with this approach to patent listing.<sup>29</sup> Moreover, individual manufacturers have argued—and we agree—that the listing of such patents in the Orange Book furthers the goals of the Hatch-Waxman Amendments by putting generic drug manufacturers on notice of the patent that could delay the sale of a generic drug product, and allowing the possible patent infringement suit to be resolved before marketing begins.<sup>30</sup> Accordingly, PhRMA believes that patents claiming a drug delivery device, including those that do not disclose or claim the active ingredient or formulation of the approved drug product, are listable in the Orange Book. We ask that FDA confirm its agreement with this conclusion as it finalizes the proposed rule.

C. Orange Book Submissions

1. *Submission of Forms FDA 3542 and 3542a*

PhRMA requests that FDA clarify several aspects of its proposals regarding Orange Book submissions on Forms FDA 3542 and 3542a. First, PhRMA requests that the agency revise the language of proposed 21 C.F.R. § 314.53(d)(4)(ii) to confirm that NDA holders may submit Form FDA 3542 through the Electronic Submissions Gateway. Although we believe this is FDA's intent,<sup>31</sup> the language of the proposed regulation and preamble refer only to submissions through the Office of Generic Drugs (OGD) Document Room. For example, FDA explains in the preamble that it is proposing that "patent information filed on Form FDA 3542 upon and after approval of an NDA or supplement be submitted directly to the Orange Book staff through the OGD Document Room."<sup>32</sup>

Second, PhRMA asks that FDA clarify in the preamble that the agency intends for applicants to submit Form FDA 3542a via CDER's Central Document Room. Although the proposed rule as amended makes this point, the preamble to the proposed rule states that "patent information submitted on Form FDA 3542a with the filing of an NDA, amendment, or

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<sup>29</sup> See Forest Labs. Advisory Opinion Request, *supra* note 24, at 5.

<sup>30</sup> *Id.* at 4; Novo Nordisk Advisory Opinion Request, *supra* note 24, at 4; Astra Zeneca Advisory Opinion Request 2007, *supra* note 24, at 3; Astra Zeneca Advisory Opinion Request 2006, *supra* note 24, at 2; GSK Advisory Opinion Request, *supra* note 24, at 2.

<sup>31</sup> We note that FDA is proposing to "change the addressee to whom submission of Form FDA 3542 should be sent from the Central Document Room to the OGD Document Room or the Electronic Submissions Gateway," 80 Fed. Reg. at 6885 (proposed 21 C.F.R. § 314.53(d)(5)), which suggests that the electronic gateway submission approach is acceptable.

<sup>32</sup> *Id.* at 6825; see also *id.* at 6885 (proposed 21 C.F.R. § 314.53(d)(4)) ("Patent information submitted upon and after approval of an NDA or supplement. The applicant must submit patent information required by paragraphs (c)(1) and (c)(2)(ii) of this section on Form FDA 3542 to the Office of Generic Drugs, OGD Document Room, Attention: Orange Book Staff, 7620 Standish Pl., Rockville, MD 20855.").

supplement, and prior to approval of the application must continue to be submitted directly to the NDA” as required under current regulations.<sup>33</sup>

With respect to delisting requests made by the NDA holder, the proposed rule includes a physical address for sending requests that were required by court order, but does not list an address for voluntary delistings.<sup>34</sup> If FDA intends for the same address to be used in both scenarios, we recommend that FDA revise the proposed rule to clarify this intent. Additionally, proposed section 314.53(f)(2)(i) indicates that the NDA holder must “promptly” notify FDA of the delisting request.<sup>35</sup> It is unclear what the agency means by “promptly,” and whether the definition would vary under different circumstances. For example, while the default for prompt notification could be thirty days, when prosecuting a reissue of a patent held invalid, it may be prudent for an NDA holder to wait to delist the original patent until the reissue patent has issued. Accordingly, we ask that FDA clarify where, and when, voluntary delisting requests should be submitted.

Third, FDA proposes to amend section 314.53 to require that the “NDA holder. . . submit on Form 3542a correction to the expiration date of the patent . . . within 30 days of receipt of a certificate of extension as described in 35 U.S.C. 156(e)(1) or documentation of an extension of the term of the patent as described in 35 U.S.C. 156(e)(2).”<sup>36</sup> PhRMA suggests that FDA clarify what the consequences are to the NDA holder and patent owner if such a submission is not made in a timely fashion.

## 2. *Proactive Posting of Form FDA 3542*

PhRMA suggests that FDA reconsider its proposal to make Form FDA 3542 publicly available on a proactive basis.<sup>37</sup> With few exceptions, this form has traditionally been obtained in narrow circumstances, either through a Freedom of Information Act (FOIA) request submitted to the agency<sup>38</sup> or in the context of litigation. Broad, proactive dissemination of Form FDA 3542 is unnecessary to fulfill the purpose of the Hatch-Waxman early resolution procedure for patent disputes, and these Forms may be confusing to the public, leading to misinterpretation of the scope of the relevant patent rights relating to the approved product or approved method of use. The forms could be misused or misinterpreted in litigation or in other commercial contexts.

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<sup>33</sup> *Id.* at 6825 (citing 21 C.F.R. §§ 314.50(h) and 314.70(f)).

<sup>34</sup> *Id.* at 6885-86 (proposed 21 C.F.R. § 314.53(f)(2)(ii)).

<sup>35</sup> *Id.* at 6885.

<sup>36</sup> *Id.* at 6886 (proposed 21 C.F.R. § 314.53(f)(2)(ii)).

<sup>37</sup> *Id.* at 6826 (“We anticipate additional requests for the information submitted on Form FDA 3542 and may elect to proactively post on FDA’s Web site a copy of Form FDA 3542 for patents listed in the Orange Book in advance of a request under the Freedom of Information Act[.]”).

<sup>38</sup> *See* 21 C.F.R. § 314.53(e).

Moreover, FDA's proposal does not specify when, or under what conditions, the agency would post Form FDA 3542 (i.e., whether FDA would post *all* copies of Form FDA 3542 or only some subset). Therefore, it appears possible that the proposal could result in disparate treatment of similarly situated parties who submit the form. For this reason and given the potential detriment that unfettered access to the form could cause to an NDA holder, PhRMA urges that FDA refrain from proactively posting copies of Form FDA 3542 on its website in advance of a FOIA request.

## II. Timing of ANDA and 505(b)(2) Application Approvals

### A. Codification of *Mylan v. Thompson*

PhRMA supports FDA's intent to codify *Mylan v. Thompson* in proposed section 314.107(g). We recommend that FDA revise the language of the proposed regulation to more clearly capture this intent.

In *Mylan*, the D.C. Circuit upheld FDA's conversion of Mylan's final approval for a generic version of Duragesic® (fentanyl transdermal system) to tentative approval. In that case, the patent holder had brought suit for patent infringement on day 46 after receiving notice of paragraph IV certification.<sup>39</sup> Thus, there was no 30-month stay. FDA subsequently approved the ANDA. Thereafter, the district court found patent infringement and ordered, under 35 U.S.C. 271(e)(4)(A), that the effective date of the ANDA be delayed until patent expiry.<sup>40</sup> FDA's conversion of the final approval to tentative approval therefore was necessary and appropriate to give effect to this court order.

Proposed section 314.107(g) provides that, if "a court enters an order requiring, in the case of an already approved 505(b)(2) application or ANDA, that the date of approval be delayed, FDA will convert the approval to a tentative approval if appropriate."<sup>41</sup> We recommend that FDA revise this language to delete "if appropriate." We also suggest that, consistent with *Mylan*, FDA clarify that "court" refers to either a district court or appellate court. PhRMA believes that section 314.107(g), with these clarifications, is appropriate to "giv[e] effect to [a] court order under 35 U.S.C. 271(e)(4), irrespective of whether the order relates to a patent associated with a 30-month stay of approval."<sup>42</sup>

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<sup>39</sup> *Mylan v. Thompson*, 389 F.3d 1272, 1277 (D.C. Cir. 2004).

<sup>40</sup> *Id.*

<sup>41</sup> 80 Fed. Reg. at 6895 (proposed 21 C.F.R. § 314.107(g)).

<sup>42</sup> *Id.* at 6865 (citing *Mylan*, 389 F.3d at 1272).

B. Approval of ANDAs and Section 505(b)(2) Applications After Expiration of 30-Month Stay

The proposed rule expressly addresses what happens if a court finds patent infringement *before*, but not *after*, expiration of a 30-month stay or 7<sup>1</sup>/<sub>2</sub>-year period. We recommend FDA revise the proposed rule to fill this gap. Specifically, section 314.107(b) should be revised to provide that FDA will not approve a pending ANDA or section 505(b)(2) application if a district court finds patent infringement *after* expiry of the 30-month stay or 7<sup>1</sup>/<sub>2</sub>-year period. PhRMA believes this approach is consistent with FDA's longstanding practice, the legislative history, and other preamble statements.

The proposed rule could be read to imply that FDA will approve a pending ANDA or section 505(b)(2) application despite a court decision of infringement, if that decision is made after expiry of the 30-month stay or 7<sup>1</sup>/<sub>2</sub>-year period. First, the proposed rule states that an ANDA or section 505(b)(2) application may be approved upon expiry of the 7<sup>1</sup>/<sub>2</sub>-year period and mentions no exceptions to this rule.<sup>43</sup> Second, the proposed regulation states that an ANDA or section 505(b)(2) application may be made effective upon expiry of the 30-month stay, “[e]xcept as provided” in paragraphs (b)(3)(iii) and (b)(3)(iv) and other provisions not relevant here.<sup>44</sup> These exceptions, in turn, apply where a district court finds patent infringement “*before* the expiration of the 30-month period, or 7<sup>1</sup>/<sub>2</sub> years where applicable.”<sup>45</sup> The proposed rule does not, however, provide an exception if patent infringement is found *after* expiry of the applicable period but prior to FDA approval. Moreover, the preamble states that “FDA is not required to delay approval of an otherwise approvable ANDA until there has been a court decision from which no appeal can be or has been taken.”<sup>46</sup> Thus, PhRMA is concerned that the proposed rule could be interpreted to mean that FDA can approve an ANDA or 505(b)(2) application—even if the district court has found patent infringement—if the 30-month stay or 7<sup>1</sup>/<sub>2</sub>-year period has expired.

In light of legislative history addressing this precise issue, precedent established by FDA, and other statements in the preamble,<sup>47</sup> we do not believe this is the desired intent. Therefore, we urge the agency to revise the regulation to state that FDA will award tentative—not final—approval to a pending ANDA or section 505(b)(2) application if the court has found infringement after expiry of the 30-month stay or 7<sup>1</sup>/<sub>2</sub>-year period. This approach would codify FDA's

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<sup>43</sup> 80 Fed. Reg. at 6893 (proposed 21 C.F.R. § 314.107(b)(3)(i)(B)).

<sup>44</sup> *Id.* at 6893 (proposed 21 C.F.R. § 314.107(b)(3)(i)(A)).

<sup>45</sup> *Id.* at 6894 (proposed 21 C.F.R. § 314.107(b)(3)(b)(iii)-(iv)) (emphasis added).

<sup>46</sup> *Id.* at 6863.

<sup>47</sup> *Id.* at 6865 (“[W]e are proposing to revise § 314.107(b)(4) to state that FDA will issue a tentative approval letter when tentative approval is appropriate in accordance with a court order pursuant to 35 U.S.C. 271(e)(4)(A) . . . , irrespective of whether the injunction relates to a patent described in § 314.107(b)(3) (see proposed § 314.107(e)(1)(vi))”).

“longstanding practice,” illustrated by FDA’s letter decision to Mylan in the Duragesic case.<sup>48</sup> There, FDA interpreted “the unqualified plain meaning of [35 U.S.C. 271(e)(4)(A)]” to indicate that, upon a finding of patent infringement, a “mandated delay of the effective date of approval takes place regardless of whether the ANDA remains pending or has obtained a final effective approval.”<sup>49</sup> This letter decision was consistent with the legislative history of the Hatch-Waxman Amendments, as summarized in the following passage from the House Report:

If the infringing party has not begun commercial marketing of the drug, injunctive relief may be granted to prevent any commercial activity with the drug and FDA would be mandated to make the effective date not earlier than the expiration date of the infringed patent . . . .<sup>50</sup>

Thus, FDA has firmly stated that, if a court finds infringement and orders that ANDA approval be delayed until patent expiry, the agency will not issue an approval letter “until the barrier to approval has expired.”<sup>51</sup> PhRMA believes that the changes described above will ensure this intent is clearly captured in the text of the regulation.

### C. GAIN Exclusivity

PhRMA requests that FDA update proposed 21 C.F.R. § 314.107(d) to reflect Generating Antibiotic Incentives Now exclusivity. The proposed rule covers delays to ANDA and 505(b)(2) application approvals due to non-patent regulatory exclusivity periods; however, it does not mention this exclusivity for designated qualified infectious disease products under section 505E of the FDCA. We recommend that FDA revise the proposed regulation to reflect that this exclusivity may delay approval of an ANDA and 505(b)(2) application and make any other necessary conforming edits to the proposed rule.

## III. **Grants of Preliminary Injunctions**

We recommend that FDA clarify its proposed regulation governing approval of an ANDA or section 505(b)(2) application where the court has entered a preliminary injunction.

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<sup>48</sup> Letter from Gary Buehler, Director of the Office of Generic Drugs, to E. Anthony Figg and Peter O. Safir (Jun. 22, 2004) (“Mylan Letter I”), at 3.

<sup>49</sup> Mylan Letter I, *supra* note 48, at 5; 35 U.S.C. § 271(e)(4)(A) (“For an act of infringement described in paragraph (2) . . . the court shall order the effective date of any approval of the drug . . . involved in the infringement to be a date which is not earlier than the date of the expiration of the patent which has been infringed”).

<sup>50</sup> H.R. Rep. No. 98-857, pt. 1 (1984), at 46.

<sup>51</sup> Mylan Letter I, *supra* note 48, at 6-7.

First, the proposed regulation addresses only situations where the preliminary injunction was granted *before*—but not *after*—expiry of a 30-month stay or 7<sup>1</sup>/<sub>2</sub>-year period. Consistent with the above, the revised regulation should provide that FDA will not approve a pending ANDA or section 505(b)(2) application where the district court enters a preliminary injunction after expiry of the stay or 7<sup>1</sup>/<sub>2</sub>-year period (unless the court decides the patent is invalid, unenforceable, or not infringed).

Similarly, the proposed regulation does not explicitly address cases where a preliminary injunction is granted *after* expiry of the 30-month or 7<sup>1</sup>/<sub>2</sub>-year period *and* the district court then finds patent infringement. We note that the preamble states, “If a preliminary injunction is entered *before* the expiration of the 30-month stay, FDA interprets section 505(j)(5)(B)(iii) of the FD&C Act to require that the stay of approval is extended until the court decides the issues of patent infringement and validity.”<sup>52</sup> We agree that the preliminary injunction is an extension of the stay. Based on this language, we believe that FDA would deem a final judgment of infringement issuing after grant of a preliminary injunction to have occurred before expiry of the stay for purposes of the regulations, even if 30 months or 7<sup>1</sup>/<sub>2</sub> years have actually elapsed. Proposed section 314.107(b)(3)(v) implies this approach by stating “[i]f the court [following the grant of a preliminary injunction] decides that the patent has been infringed, the 505(b)(2) application or ANDA may be approved as provided in paragraph (b)(3)(iii) or (b)(3)(iv) of this section . . . .”<sup>53</sup> The cross-referenced paragraphs address situations where the district court finds patent infringement *before* expiry of the 30-month or 7<sup>1</sup>/<sub>2</sub> year period. They also provide that the stay continues through appeal of the district court decision. Consistent with the above, we ask FDA to make explicit in its final regulations that the issuance of a preliminary injunction after expiry of the 30-month or 7<sup>1</sup>/<sub>2</sub>-year period, combined with a district court finding of infringement, stays approval through at least the appeal.

As a related issue, PhRMA also suggests that the final rule address how FDA will regard an applicant’s voluntary agreement not to launch or to provide pre-launch notice, if the court requested such agreement in lieu of issuing a preliminary injunction. PhRMA believes that, for purposes of the rule, FDA should treat these agreements as equivalent to a preliminary injunction and thereby similarly extend the 30-month stay or 7<sup>1</sup>/<sub>2</sub>-year period. The agency’s adoption of this position is consistent with the conclusion stated in the preamble that a preliminary injunction—and therefore an agreement that serves as the equivalent of a preliminary injunction—extends the stay of approval.

#### **IV. Patent Certifications for Certain ANDA and 505(b)(2) Supplements**

FDA notes in the preamble to the proposed rule that it “is not proposing to require a patent certification with a supplement to change the formulation or to change the physical form

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<sup>52</sup> 80 Fed. Reg. at 6864 (emphasis added).

<sup>53</sup> *Id.* at 6894 (proposed 21 C.F.R. § 314.107(b)(3)(B)(v)).

or crystalline structure of the active ingredient of a product approved in a 505(b)(2) application or ANDA.”<sup>54</sup> PhRMA respectfully disagrees with this position. This proposal would create a gap in the regulations that an applicant could exploit by first seeking approval of an ANDA or 505(b)(2) application for a product that it does not intend to market, followed by a supplement to the approved application for a different formulation or physical form or crystalline structure that it does intend to market. Through this approach, an applicant could circumvent the statutory requirements: (1) to file a paragraph IV certification, (2) to provide notice of these changes to the patent holder, which can lead to litigation of related patent issues, potentially subject to a 30-month stay. Indeed, FDA cited similar concerns in proposing to require that applicants file new certifications for *amendments* to pending applications describing major formulation changes; the rules should not be different when these changes are instead proposed in a supplement to an approved application.<sup>55</sup>

As the preamble to the proposed rule notes in discussing Biovail Corporation’s 2003 citizen petition, “the factual and legal basis of the applicant’s opinion that the patent will not be infringed may have changed in light of the changes in product formulation.”<sup>56</sup> This analysis supports requirements of patent certification and notice for supplements seeking approval of a new strength or condition of use, as FDA has proposed,<sup>57</sup> but it applies even more directly to supplements for non-minor changes in formulation or changes in physical form or crystalline structure. Contrary to the preamble’s assertion, an NDA holder or patent owner’s monitoring of an ANDA or 505(b)(2) application’s postapproval changes is not sufficient to substitute for a patent certification, notice, and the opportunity to litigate any patent infringement claims raised by the ANDA or 505(b)(2) supplement with the potential for a stay.<sup>58</sup> Moreover, FDA’s statement in the preamble seems to assume that the applicant would actually market the original formulation or physical form and therefore, that the NDA holder could detect the changes by monitoring the applicant’s product in the marketplace. It does not account for the possibility that applicants may seek approval of products they do not intend to market and supplement the approved ANDA or section 505(b)(2) application to reflect the actual, to-be-marketed product.

Therefore, PhRMA recommends that FDA amend the proposed rule to require ANDA and 505(b)(2) applicants to submit patent certifications for supplements that propose major changes to the formulation or changes to the physical form or crystalline structure of the active

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<sup>54</sup> *Id.* at 6848.

<sup>55</sup> *Id.* at 6849 (“By requiring a new patent certification and, with respect to a paragraph IV certification, a new notice of paragraph IV certification to be sent at the same time the amendment for the change in formulation is submitted to FDA, we aim to uphold the legislative balance of the Hatch-Waxman Amendments that facilitates the availability of generic drug products while protecting innovator intellectual property rights”).

<sup>56</sup> *Id.* at 6847-6848.

<sup>57</sup> *See id.* at 6887, 6891 (proposed 21 C.F.R. §§ 314.30(i), 314.97(c)).

<sup>58</sup> *See id.* at 6848.

ingredient. This approach accords with the text of the FDCA that requires an “application” submitted under section 505(b)(2) or 505(j) to include a patent certification, given that FDA defines “application” to include supplements.<sup>59</sup> The statute also explicitly contemplates the submission of patent certifications for ANDA and 505(b)(2) supplements.<sup>60</sup> We therefore urge FDA to change the proposed regulation as described.

## V. Listed Drug Cited by 505(b)(2) Applicant

PhRMA supports the proposed revision of section 314.54(a)(1)(iii) to require that a 505(b)(2) applicant identify, as a listed drug, any approved product that (1) is pharmaceutically equivalent to the proposed product and (2) was approved before submission of the 505(b)(2) application.<sup>61</sup> As FDA explains in its preamble to the proposed rule, this requirement is “intended 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 as an ANDA—namely, submission of a patent certification for a listed patent that corresponds to the protected aspects of the pharmaceutically equivalent listed drug.”<sup>62</sup>

We urge FDA to expand this requirement to apply in additional situations, including—contrary to the preamble—“if a pharmaceutically equivalent product is approved while the 505(b)(2) application is pending.”<sup>63</sup> Just as FDA is proposing to require for ANDA applicants, a 505(b)(2) applicant should be required to file a new application citing a pharmaceutical

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<sup>59</sup> FDCA §§ 505(j)(2)(A)(vii); 505(b)(2)(A); 21 C.F.R. § 314.3(b) (“Application means the application described under §314.50, including all amendments and supplements to the application.”).

<sup>60</sup> See FDCA §§ 505(j)(2)(B)(ii)(II) (“An applicant that makes a certification described in subparagraph (A)(vii)(IV) shall give notice . . . if the certification is in an amendment *or supplement* to the application . . . regardless of whether the applicant has already given notice with respect to another such certification contained in the application or in an amendment or supplement to the application.”) (emphasis added) and 505(b)(3)(B)(ii) (“An applicant that makes a certification described in paragraph (2)(A)(iv) shall give notice . . . if the certification is in an amendment *or supplement*, regardless of whether the applicant has already given notice with respect to another such certification contained in the application or in an amendment or supplement to the application.”) (emphasis added).

<sup>61</sup> 80 Fed. Reg. at 6886 (proposed 21 C.F.R. § 314.54(a)(1)(iii)). The preamble includes a passage that could give the misimpression that complex drugs can qualify as pharmaceutical equivalents even when they cannot be proven the “same” as one another. The passage begins by stating that “[t]here are circumstances in which a proposed drug product that is pharmaceutically equivalent to a listed drug . . . is not eligible for approval as an ANDA” and then lists examples, including “[f]or certain complex drug products, an applicant may be unable to demonstrate ‘sameness’ of the active ingredient as required for submission of an ANDA.” See *id.* at 6855-56. The context of this passage implies that pharmaceutical equivalence can be established even when two products cannot be shown to be the same. This implication is inconsistent with FDA’s definition of “pharmaceutical equivalents” as drug products that “contain the same active ingredient(s) . . .” *Orange Book* (35th ed. 2015) at vii. PhRMA recommends that FDA clarify this passage to convey that pharmaceutical equivalence is not possible if sameness cannot be established.

<sup>62</sup> 80 Fed. Reg. at 6856.

<sup>63</sup> *Id.*



equivalent as a listed drug if the agency approves that product *after* the 505(b)(2) application is submitted.<sup>64</sup> Like the ANDA applicant, the sponsor of a 505(b)(2) application will receive notice of the pharmaceutical equivalent's approval based on FDA's publication of that approval in the Orange Book.<sup>65</sup> Without the requirement to cite the pharmaceutical equivalent as a listed drug, the applicant would not be required to certify to the patents listed for the pharmaceutical equivalent and provide notice of this certification, with the opportunity for the patent holder to sue for infringement and be granted a 30-month stay of the 505(b)(2) application's approval while the case is litigated. The current proposal would result in the sponsor of the pharmaceutical equivalent approved after submission of a section 505(b)(2) application, simply by virtue of timing, to have no viable option for protecting its intellectual property rights before launch of the pharmaceutical equivalent. FDA recognized this point in proposing to require that ANDA applicants change the basis for their ANDA submissions upon approval of a pharmaceutical equivalent.<sup>66</sup> Likewise, our suggested approach will ensure that NDA holders have a reasonable opportunity to obtain a single 30-month stay and that any non-patent exclusivity applicable to the NDA for the pharmaceutical equivalent is meaningful.

For similar reasons, PhRMA suggests that the requirement also apply to a 505(b)(2) applicant whose proposed drug is a pharmaceutical alternative of, although not pharmaceutically equivalent to, a listed drug. Establishing such a requirement would help to achieve the objective articulated by FDA of preventing the use of the 505(b)(2) pathway to avoid the statutory obligations imposed on ANDA applicants, including section 505(b)(2) applicants who may be eligible to submit suitability petitions. The recent section 505(b)(2) application for a pharmaceutical alternative to Colcrys® (colchicine) 0.6-milligram tablets and the related litigation highlight that our concern is not speculative. There, West-Ward Pharmaceuticals Corp. filed a section 505(b)(2) application for 0.6-milligram colchicine *capsules*. Despite the similarities to Colcrys in strength and active ingredient, West-Ward cited Col-Probenecid, a tablet containing 0.5 mg of colchicine and 500 mg of probenecid, as the listed drug. As the district court noted, “[i]t is undisputed that West-Ward wanted to cite Col-Probenecid instead of Colcrys because, unlike Colcrys, Col-Probenecid is not tied to any patents that would require

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<sup>64</sup> *See id.* at 6853.

<sup>65</sup> *Id.* (citation omitted).

<sup>66</sup> *Id.* (“FDA’s requirement that an applicant with a pending ANDA must change its basis for ANDA submission upon approval of an NDA for the same drug product described in the suitability petition also is intended to ensure that ANDA applicants do not circumvent the patent certification requirements . . . . Otherwise, if a patent were listed for a drug product approved in an NDA and designated as the RLD and a pending ANDA submitted pursuant to an approved suitability petition were permitted to amend its application to refer to the new RLD, even a single 30-month stay would not be available . . . . In addition, our policy appropriately protects any marketing exclusivity that has been granted to the newly approved RLD.”).

West-Ward to submit a Paragraph IV certification.”<sup>67</sup> PhRMA believes that such intentional end-runs around the statutory patent certification requirements should not be permitted.

## VI. Notification of Settlement Agreements

PhRMA agrees with FDA’s proposed approach, described in the preamble, to “require submission of written documentation that the parties have entered into a settlement that has terminated . . . patent infringement litigation, but . . . not require applicants to send copies of the actual settlement agreement to FDA.”<sup>68</sup> PhRMA recommends that FDA revise the language of proposed section 314.107(e)(iv) to more clearly capture FDA’s intent that the settlement agreements themselves not be submitted and to describe the contents of the documentation FDA envisions will be submitted.

As proposed, section 317.107(e)(iv) could be misinterpreted to require submissions of the settlement agreements themselves, notwithstanding FDA’s preamble statement. Proposed section 314.107(e)(iv) would require applicants to submit to FDA “[a] copy of any documented agreement described in paragraph (b)(3)(vi) of this section.”<sup>69</sup> Paragraph (b)(3)(vi), in turn, refers to “[w]ritten consent” in which the a patent owner or exclusive patent licensee “agrees in writing” to the approval of a 505(b)(2) application or ANDA at any time on or after the date of the consent.<sup>70</sup> We recommend that FDA clarify, in the text of the regulation itself, that “documented agreement” does not refer to the settlement agreement, and that these agreements need not be submitted. These agreements contain confidential settlement terms and require that parties not disclose details about their respective agreements. Even the prospect that such agreements could be disclosed could complicate settlement negotiations or deter parties from reaching settlement.

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<sup>67</sup> *Takeda Pharm., U.S.A., Inc. v. Burwell*, No. 14-1668 , 2015 WL 252806, at \*8 (D.D.C. Jan. 13, 2015), *appeal docketed*, No. 15-5021 (D.C. Cir. Jan. 26, 2015). PhRMA firmly disagrees with statements in this district court opinion suggesting that FDA may access data submitted in another sponsor’s NDA in its review of a section 505(b)(2) application. *See, e.g., id.* at \*16 (“[I]t makes little sense to suggest, as Takeda does, that FDA cannot consider the previously-submitted safety and effectiveness data of third-party drug sponsors as part of its review of a Section 505(b)(2) application without securing the data owner’s permission. Surely the prior applicant’s voluntary submission of its proprietary data to FDA waived any right that applicant may have had to prohibit FDA from ‘open[ing] th[e] locked file drawer’ to access the applicant’s data in the future.”). PhRMA believes that these statements conflict with FDA’s longstanding position that it relies on the public finding of safety and effectiveness for a listed drug, not the data in the listed drug NDA, in approving 505(b)(2) applications. In any case, PhRMA believes that the court’s statements are inconsistent with FDA’s legal obligations to protect trade secrets and confidential commercial information submitted to the agency in NDAs.

<sup>68</sup> 80 Fed. Reg. at 6867.

<sup>69</sup> *Id.* at 6894 (proposed 21 C.F.R. § 314.107(e)(iv)).

<sup>70</sup> *Id.* (proposed 21 C.F.R. § 314.107(b)(3)(vi)).

With respect to the content of the required documentation, we ask that FDA address the following issues:

- Does FDA envision the submission of a particular form to serve as notification of the settlement agreement? If so, what will be the content of that form?
- If FDA does not envisage use of a particular form for this notification and the only document that outlines the consent to early launch is the actual settlement agreement, what information should be included in the settlement notification? For instance, should the parties submit a joint letter to FDA that summarizes the consent language?

PhRMA asks FDA to clarify these details to avoid misinterpretations of the proposed requirement, which could cause complications in providing sufficient notice to the agency.

## VII. Definition of “Date of Approval”

PhRMA recommends that FDA abandon its proposal to amend and relocate the definition of “date of approval” that currently appears in the new drug product exclusivity regulation at 21 C.F.R. 314.108(a). Although we understand the proposed changes to this definition are meant to be ministerial,<sup>71</sup> we believe the proposal would substantively change the regulations in a manner that would harm incentives for innovation.

FDA proposes to amend its definition of “date of approval” to mean “the date on the approval letter from FDA stating that the NDA or ANDA is approved.”<sup>72</sup> This amended definition would be moved from its current position in section 314.108(a) to section 314.3(b) and would no longer include the qualification that the date of approval is the date on the approval letter “whether or not final printed labeling or other materials must still be submitted *as long as approval of such labeling or materials is not expressly required.*”<sup>73</sup>

PhRMA asks FDA to refrain from making these changes. The definition’s current place in section 314.108(a) illustrates its direct bearing on the interpretation and operation of the new product exclusivity provisions in the remainder of 21 C.F.R. 314.108. Moreover, the language proposed for deletion (“as long as approval of such labeling or materials is not expressly required”) is not already captured in section 314.105(b), as suggested by the preamble,<sup>74</sup> or by

<sup>71</sup> See *id.* at 6812 (“These proposed revisions to the definition of ‘date of approval’ are not intended to alter our interpretation of § 314.108”).

<sup>72</sup> *Id.* at 6877 (proposed 21 C.F.R. § 314.3(b)).

<sup>73</sup> 21 C.F.R. § 314.108(a) (emphasis added).

<sup>74</sup> 80 Fed. Reg. at 6813; 21 C.F.R. § 314.105(b) (“FDA will approve an application and issue the applicant an approval letter on the basis of draft labeling if the only deficiencies in the application concern editorial or similar (continued...)”).

any other provision in FDA's regulations. Instead, PhRMA believes that this language serves a distinctive purpose by recognizing the circumstances in which the date of FDA's approval of an NDA is not the same as the date on which an approved NDA's exclusivity period begins to run. Removing this qualifier from the existing definition of "date of approval" would constitute a change to the regulation, with much more significant implications than the preamble suggests.

PhRMA also suggests that the agency take this opportunity to clarify the application of its regulatory definition of "date of approval" with respect to drug products subject to controlled substance scheduling by the Drug Enforcement Administration (DEA), at least for purposes of determining the start dates of these drugs' new chemical entity (NCE) exclusivity periods. Specifically, as we have stated in the past, PhRMA believes FDA should define the "date of approval" for purposes of NCE exclusivity of controlled substances as the date on which the company could begin commercially marketing the drug—not the date stamped on the NDA approval letter.<sup>75</sup> Although FDA has denied citizen petitions to this effect, these issues remain the subject of active litigation<sup>76</sup> and have important implications for incentives to innovate. The scheduling of a drug sometimes is not completed until substantially after FDA has approved the drug as safe and effective.<sup>77</sup> This delay in turn pushes back the date on which the sponsor can market the approved drug, reducing the effective NCE exclusivity period to less than five years. The discrepancy between the date on which an approval letter is issued and the date on which a drug can be introduced into interstate commerce creates significant commercial uncertainty for sponsors and undermines the NCE exclusivity period as an incentive to promote innovation. PhRMA therefore urges the agency to bridge the existing gap through regulation in light of the pressing policy concerns outlined above.

## VIII. Administrative Issues

### A. Designated Delivery Service

The proposed rule would require that applicants send notice of each paragraph IV certification by registered or certified mail, return receipt requested, or by a "designated delivery

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minor deficiencies in the draft labeling. Such approval will be conditioned upon the applicant incorporating the specified labeling changes exactly as directed, and upon the applicant submitting to FDA a copy of the final printed labeling prior to marketing.")

<sup>75</sup> PhRMA, Comments on Citizen Petition of Eisai, Inc., Docket No. FDA-2013-P-0884 (Mar. 10, 2014). Products that require controlled substance scheduling can be introduced into interstate commerce after the product labeling incorporates the schedule as finalized by the DEA.

<sup>76</sup> Complaint, *Eisai, Inc. v. Burwell*, Case No. 1:14-cv-01346 (D.D.C. Aug. 8, 2014).

<sup>77</sup> See *Eisai, Inc.*, Citizen Petition, Docket No. FDA-2013-P-0884 (Jul. 25, 2013), at 9; *UCB, Inc.*, Citizen Petition, Docket No. 2013-P-1397 (Nov. 18, 2013), at 2-3.

service.”<sup>78</sup> According to the proposed rule, FDA “will periodically issue guidance regarding designated delivery services” that meet the criteria established in the definition of this term.<sup>79</sup>

PhRMA requests that the agency clarify whether applicants must use only the services identified in periodic guidance as “designated delivery services” or if they may rely on a delivery service that they believe satisfies the criteria set out in the proposed rule, even if the service has not been specifically described as such in periodic guidance. We would also appreciate clarification of whether, in those instances where the service has not been described in a periodic guidance, FDA pre-approval of the particular delivery service is required before it can be used by an applicant.

B. Names and Addresses for Notice of Paragraph IV Certification

Like the current regulations, the proposed rule refers applicants to the U.S. Patent and Trademark Office and Orange Book Staff for information on the names and addresses of the patent holder and NDA holder, respectively, to whom notice of a paragraph IV certification must be sent.<sup>80</sup> PhRMA urges the agency’s Orange Book staff to consider maintaining and publishing names and addresses of record for each patent owner and NDA holder to ensure that 505(b)(2) and ANDA applicants are able to satisfy the notice requirement. This approach would ensure that notice letters are received by the appropriate person at the appropriate corporate entity. PhRMA further requests that FDA revise the proposed regulations to provide that failure to send notice letters to these designated names and addresses of record will render the notice invalid, and the 45-day clock for bringing suit will not begin until valid notice has been provided to the names and addresses of record.

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<sup>78</sup> 80 Fed. Reg. at 6881 (proposed 21 C.F.R. § 314.52(a)).

<sup>79</sup> *Id.* at 6882, 6891 (proposed 21 C.F.R. § 314.52(g), 314.95(g)).

<sup>80</sup> *Id.* at 6881, 6889 (proposed 21 C.F.R. §§ 314.52(a), 314.95(a)).

Food and Drug Administration  
Comments of the Pharmaceutical Research and Manufacturers of America  
Docket No. FDA-2011-N-0830  
June 8, 2015

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PhRMA looks forward to continued collaboration with FDA on the implementation of the MMA and would welcome the opportunity to discuss these comments further.

Sincerely,

A handwritten signature in blue ink, appearing to read "David E. Korn". The signature is fluid and cursive, with a large initial "D" and "K".

David E. Korn

cc: James M. Spears, Executive Vice President, General Counsel and Secretary, PhRMA  
Jeffrey K. Francer, Vice President & Senior Counsel, PhRMA