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August 31, 2020

SUBMITTED ELECTRONICALLY

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2020-N-1127: Listing of Patent Information in the Orange Book; Establishment of a Public Docket; Request for Comments

Dear Sir or Madam:

The Pharmaceutical Research and Manufacturers of America ("PhRMA") is pleased to provide comments to the U.S. Food and Drug Administration ("FDA" or the "Agency") on the questions regarding patent listing in the above-referenced docket.[1] 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. Since 2000, PhRMA member companies have invested more than $900 billion in the search for new treatments and cures, including an estimated $79.6 billion in 2018 alone.

The Drug Price Competition and Patent Term Restoration Act of 1984, also known as the Hatch-Waxman Amendments (or simply Hatch-Waxman), was intended both to increase patient access to generic medicines and to preserve incentives to develop new medicines that address unmet medical needs and enhance patients' lives. Hatch-Waxman, including the existing patent listing framework, has been a clear success in fostering competition by expediting the entry of generic drugs. For example, generics now make up to 90% of prescriptions dispensed, up from 75% in 2009.[2] For brand medicines with annual sales greater than $250 million that faced generic entry in 2013-2014, generics captured an average of 93% of the market (by volume) within a year of entry,[3] and multiple generic applicants typically challenge listed patents as soon as they are able to do so. As described further below, to advance the balance reflected in Hatch-Waxman and the benefits it offers to patients, FDA should weigh the impact of any changes to its current patent listing practices against not only the availability of lower-cost generic drugs, but also the incentives for innovation—including with regard to novel delivery systems. These innovations provide meaningful benefit for patients, such as ensuring delivery of the correct dose, facilitating convenient at-home administration of drugs, improving compliance with drug regimens, and allowing tracking of drug administration,

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[1] 85 Fed. Reg. 33,169 (June 1, 2020).

[2] IQVIA Institute for Human Data Science, *Medicines Use and Spending in the U.S. A Review of 2018 and Outlook to 2023*, at 5 (May 2019).

[3] Grabowski H, Long G, Mortimer R, Boyo A. *Updated Trends in US Brand-Name and Generic Drug Competition*. J Med Economics. 2016;19(9):836-844 (2008 dollars).

among many other benefits. Especially in the midst of a global pandemic, in which the world is looking to the pharmaceutical industry to develop life-saving treatments and vaccines, encouraging innovation is more important than ever.

With these principles in mind, PhRMA responds to the general and specific questions provided in the Federal Register notice in the below sections I and II, respectively. In brief, PhRMA urges FDA to clarify that patents claiming the device constituent of a drug-device combination product approved in a new drug application ("NDA") or a component thereof are drug product patents subject to Orange Book listing requirements. Listing these patents advances the objectives of Hatch-Waxman. Similarly, patents claiming a method of using a device constituent or component thereof in an NDA-approved single-entity combination product are subject to Orange Book listing requirements. Furthermore, in keeping with the statutory language and FDA's ministerial role in patent listing matters, patents ought not to be excluded from Orange Book listing simply because they relate to a risk evaluation and mitigation strategy ("REMS"). Finally, PhRMA recommends that FDA consider patent listing policy issues for digital health technologies after further development of the regulatory framework for these products.

I. Responses to General Questions (Federal Register Questions A.1–A.5)

Orange Book listing of drug and method-of-use patents is a fundamental part of the Hatch-Waxman framework. The Federal Food, Drug, and Cosmetic Act ("FDCA") requires an NDA to include information regarding "any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug."[4] FDA then publishes patent information in the Orange Book. This public listing furthers Congress's intent that Hatch-Waxman strike a balance between the competing interests of innovators and generic companies. Specifically, patent listing provides: transparency as to the existence of relevant drug and method-of-use patents; an opportunity for patent litigation subject to a 30-month stay of generic approval, which allows for early, efficient, and orderly resolution of patent issues prior to marketing of the proposed generic product; and the potential for 180-day exclusivity for generic first applicants, which incentivizes patent challenges.

More specifically, as FDA has recognized, Orange Book listing of drug and method-of-use patents under the statute alerts potential generic filers to drug and method-of-use patents that could reasonably be asserted based on commercial marketing of a generic product. The Orange Book thus streamlines efforts to identify patents that could affect the market entry of a generic drug and facilitates generic applicants' analysis of patent issues. Listing drug and method-of-use patents in the Orange Book therefore reduces the likelihood that generic applicants will fail to identify an applicable drug or method-of-use patent before bringing a generic drug product to market and become liable for damages for patent infringement and/or be subject to injunctive relief. In contrast, new restrictions on patent listing could harm

[4] FDCA § 505(b)(1); *see also id.* § 505(c)(2).

abbreviated applicants by increasing the costs and burdens needed to identify relevant drug and method-of-use patents.

The Federal Register notice suggests that FDA has concerns that patent listing "creates the possibility of a stay of approval" of an abbreviated application.[5] The stay operates only upon submission of a paragraph IV certification to a listed patent and initiation of a patent infringement action within 45 days after receiving notice of the paragraph IV certification. If the innovator decides not to file suit at this time, for example, the generic company will receive the mentioned benefits of Orange Book listing, both parties will avoid litigation expenses, and no stay will apply.[6] If instead the generic applicant elects to wait until a listed patent expires to launch its product, it will file a paragraph III certification and the application cannot be approved until patent expiry.[7] A novel policy to limit patent listing would undermine the important policy objectives served by paragraph III certifications by reducing the number of patents for which paragraph III certifications would be filed. This result would undermine the notice function of patent listing in this context and the policy objectives served by the requirement that the generic applicant wait to market its product until the relevant patent—which it has chosen not to challenge—has expired.

Moreover, the stay was an important part of the grand bargain reflected in the Hatch-Waxman framework, which benefits both innovators and generic applicants.[8] Overall, the framework benefits generic companies by allowing them to rely on the findings of safety and effectiveness supported by innovator research and development to obtain approval of generic drugs, to seek approval to market prior to patent expiration, to begin the patent resolution process before they have made substantial investments in generic products, and to resolve patent disputes without potential exposure to damages. Alternatively, it allows a generic company to state, through the filing of a paragraph III certification, that it does not intend to enter the market until expiration of the patent, which helps manage its plan for market entry. The framework also benefits innovators by giving them an opportunity to enforce or defend their patents before launch of a potentially infringing product.

In particular, the stay operates in conjunction with other provisions enacted as part of Hatch-Waxman: (1) the provision overruling the 1984 *Bolar* case and providing that generic development activities relating to FDA approval do not constitute patent infringement ("the

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[5] 85 Fed. Reg. at 33,172.

[6] In contrast, under a novel policy to limit patent listing, the generic applicant would need to launch without certainty as to whether it infringes a non-listed patent.

[7] FDCA §§ 505(c)(3)(B), 505(j)(5)(B)(ii); *see* H.R. REP. NO. 98-857, pt. 1, at 15 (1984) ("Generic copies of these drugs may be approved when the patents expire unless the generic company certifies that the patent is invalid or will not be infringed").

[8] *See* H.R. REP. NO. 98-857, pt. 1, at 28 (1984); *see also* 130 Cong. Rec. 24,430 (1984) (statement of Rep. Waxman) (in opposing amendment to shorten the stay to eighteen months, stating "it was agreed upon to have a period of time by which there most likely would have been a court adjudication of the patent in question"); *id*. at 24,429 (statement of Rep. Madigan) (noting that the proposed amendment to shorten the stay period "takes away part of this compromise").

Bolar provision");[9] and (2) the provision defining the submission of an abbreviated application with a paragraph IV certification as an act of patent infringement.[10] These provisions together facilitate early, orderly resolution of patent issues before the generic drug is approved—a benefit to both parties. Specifically, the *Bolar* provision allows development activities to begin early; the "artificial" act of infringement allows litigation to start while FDA reviews the generic application rather than on the eve of launch of an approved but potentially infringing product; and the stay provides both parties with a period of time to resolve patent disputes before launch of a potentially infringing product. The efficiencies of allowing the FDA review and patent dispute resolution processes to proceed in parallel, rather than sequentially, have demonstrably contributed to the expansion of the generic marketplace and earlier access to generic drugs at the end of patent protected periods. Therefore, FDA must consider the potential for any novel patent listing policies to disrupt the established Hatch-Waxman patent listing and challenge processes—with regard to both patents for which paragraph III certifications would be filed and patents for which paragraph IV certifications would be filed.

PhRMA recognizes that certain clarifications about the limitations of patent listing would be helpful. For example, FDA should expressly state that NDA applicants and holders are not required to list patents owned by an unrelated third party, i.e., patents not owned by the NDA applicant or holder or its licensor. This clarification would be consistent with the statutory and regulatory requirements for Orange Book listing since such patents could not reasonably be asserted by the NDA holder or its licensor if an unlicensed person engaged in the manufacture, use, or sale of the drug. This clarification also would align with the purpose of the Orange Book: to list drug and method-of-use patents in order to identify drugs that might be the subject of an abbreviated application and facilitate early resolution of patent disputes between innovators and generic companies.[11] FDA can thus help ensure that patent listing is not overbroad by confirming that third party patents neither owned by nor licensed to NDA applicants and holders need not be listed in the Orange Book.

Adding new limitations on patent listing would not only disturb the grand bargain of Hatch-Waxman, but also would disrupt the orderly patent resolution process that exists under Hatch-Waxman. If certain patents were no longer required to be listed, generic companies would not be given notice of drug and method-of-use patents they might infringe by launching a follow-on product. But because innovators could still enforce these patents upon generic launch as a matter of right, generic companies would be potentially subject to damages for infringement, creating uncertainty in the marketplace. Increased reliance on this alternative patent enforcement process at the time of generic launch would involve costly, time-pressured actions for preliminary injunctions that could undermine district courts' established procedures for management of Hatch-Waxman patent litigation. Under this alternative process, a generic

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[9] 35 U.S.C. § 271(e)(1) (exempting from patent infringement otherwise infringing conduct "solely for uses reasonably related to the development and submission" of an application to FDA) (overruling *Roche Prods., Inc. v. Bolar Pharm. Co., Inc.*, 733 F.2d 858 (Fed. Cir. 1984)).

[10] 35 U.S.C. § 271(e)(2)(A).

[11] *See* H.R. REP. NO. 98-857, pt. 1, at 30 (1984) (describing the Orange Book as a "list of drugs eligible for consideration in an ANDA").

drug sponsor might launch "at risk" before the resolution of patent litigation at the district court level, depriving innovators of the opportunity to enforce or defend their patents prior to launch, a benefit that Hatch-Waxman was meant to provide.[12] An at-risk launch would require the parties to litigate damages-related issues, which would increase the cost, time, and complexity of patent litigation and potentially subject generic applicants to significant damages. Indeed, although presently rare, at-risk launches have proven costly for generic companies who later lose the underlying patent case.[13] Restricting the number of listed patents also would limit opportunities for generic applicants to obtain 180-day exclusivity by submitting a paragraph IV certification to a listed patent and thereby undermine the incentive for these applicants to challenge patents and file applications on the first day possible.[14] Indeed, without the opportunity for 180-day exclusivity, generic applicants might not invest in developing a product at all. Overall, novel restrictions on patent listing would disrupt established patent resolution procedures and tax the resources of the parties and the courts.

In any case, reducing the number of listed patents—and therefore the number of patents that potentially could give rise to a stay—is unlikely to speed up generic market entry. At-risk launches have been relatively rare (likely because potential damages could be significant). As noted by Representative Waxman in 1984, "[a]s a practical matter, the generic drug manufacturers have told us they wait for a court decision before they will market a drug."[15] In a 2002 report that discussed 30-month stays (among other things), the Federal Trade Commission (FTC) concluded that "[o]ne 30-month period to resolve disputes over patents listed in the Orange Book prior to the ANDA's filing date appears unlikely to delay generic entry . . . because it historically has approximated . . . the duration of a patent lawsuit."[16] This point remains true today: the average time to bench trial in a Hatch-Waxman paragraph IV patent litigation in those courts where the most cases are filed exceeds 30 months at 32.3 months.[17] Thus, even if FDA adopted a new policy to limit patent listings and therefore, stays, the fact that it could approve ANDAs immediately is unlikely to result in earlier generic competition. Hatch-

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[12] *See* H.R. REP. NO. 98-857, pt. 1, at 28 (1984) (explaining that the procedure for commencing a legal action for patent infringement before the generic maker has begun marketing "fairly balances the rights of a patent owner to prevent others from making, using, or selling its patented products and the rights of third parties to contest the validity of a patent or to market a product which they believe is not claimed by the patent").

[13] *See*, *e.g.*, GaBI, *Apotex clopidogrel at-risk launch costs US $442 million*, http://www.gabionline.net/Generics/News/Apotex-clopidogrel-at-risk-launch-costs-US-442-million (Feb. 3, 2012).

[14] *See* FDCA § 505(j)(5)(B)(iv)(II)(bb) (definition of "first applicant").

[15] 130 Cong. Rec. 24,430 (1984) (statement of Rep. Waxman).

[16] FTC, *Generic Drug Entry Prior to Patent Expiration: An FTC Study*, at 39 (July 2002).

[17] Docket Navigator Analytics, DOCKET NAVIGATOR (2020), https://search.docketnavigator.com/patent/search/patent_milestones (search for District Courts in Delaware and New Jersey and Case Filing Date: on or after 01/01/2017 and Type of Document: complaints (ANDA) and Type of Document: judgment (clerk and judge)). Docket Navigator bases bench trial milestones on events that typically occur near the time of a bench trial, such as the issuance of Findings of Fact and Conclusions of Law, not the actual date(s) of trial.

Waxman also contains built-in safeguards to ensure that the stay is not unduly long: the 30-month stay ends early if the generic applicant wins the patent case,[18] and the court can shorten the stay if the innovator "failed to reasonably cooperate in expediting the action."[19] Moreover, pursuant to the amendments made to Hatch-Waxman in 2003, Congress imposed a limit of one 30-month stay per ANDA, regardless of the number of listed patents that cover the generic medicine described in the ANDA (unless the generic applicant's actions trigger an exception).[20]

Finally, in considering its patent listing practices, FDA should be mindful of the criticality of robust incentives for continued biopharmaceutical innovation. On average, it takes 10 to 15 years and costs $2.6 billion to develop a new medicine.[21] Intellectual property (IP) protections, including patents, are key to supporting continued future innovation in the long term, especially given the significant scientific and regulatory risk associated with drug development—only 12% of compounds reaching clinical trials are ultimately approved.[22] Yet, with regard to patents, incentives for innovation have weakened over time. Over the years since enactment of Hatch-Waxman, patent challenges from generic applicants (in the form of paragraph IV certifications) have been filed more frequently and even further in advance of patent expiration dates. Today, many are filed as soon as possible under the statute—in the case of a new chemical entity, as early as four years after approval.[23] The market exclusivity period before first generic entry for small molecules has declined over time such that brand medicines have faced generic competition at just over twelve years after brand launch, even though the basic patent term is twenty years.[24] Additionally, the patent system itself is a source of uncertainty, due in part to Supreme Court rulings on patent eligibility[25] and increased use of the *inter partes* review (IPR) process at the U.S. Patent and Trademark Office (with some petitions filed even before the four-year mark after approval of the innovator's new chemical entity). As a

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[18] *See* FDCA § 505(c)(3)(C)(i) & (j)(5)(B)(iii)(I).

[19] FDCA § 505(c)(3)(C) & (j)(5)(B)(iii).

[20] *See* FDCA §§ 505(c)(3)(C) & 505(j)(5)(B)(iii) (establishing that to trigger the 30-month stay, an action must be brought for "infringement of the patent that is the subject of the certification and for which information was submitted to the Secretary under subsection (b)(1) or (c)(2) before the date on which the application (excluding an amendment or supplement to the application) . . . was submitted").

[21] DiMasi JA, Grabowski HG, Hansen RW. *Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs*. J Health Econ. 2016;47:20-33 (2013 dollars); PhRMA, Research & Development, https://www.phrma.org/en/Advocacy/Research-Development.

[22] DiMasi, *supra* note 20.

[23] *See* FDCA §§ 505(c)(3)(C)(ii) & 505(j)(5)(B)(ii) (permitting filing of an abbreviated application with a paragraph IV certification four years after the approval of a drug with new chemical entity exclusivity); *see also* Grabowski, *supra* note 3.

[24] Grabowski, *supra* note 3, at 843 (for drugs experiencing generic entry in 2013-2014, the market exclusivity period was 12.5 years for drugs with sales greater than $250 million in the year prior to generic entry, and for all drugs included in the study, the average market exclusivity period was 13.6 years)

[25] Rulings by the Court of Appeals for the Federal Circuit, such as the double patenting decision in *Gilead Sciences, Inc. v. Natco Pharma Ltd.*, 753 F.3d 1208 (Fed. Cir. 2014), *cert. denied* 575 U.S. 902 (2015), have also increased uncertainty as to the degree of patent protection available for companies.

result, the current IP framework can create challenges for innovative companies looking to develop new products. FDA should ensure that any changes to its patent listing practices promote, rather than undermine, incentives for innovation, consistent with the goals of Hatch-Waxman.

As explained further below, to these ends, PhRMA believes, consistent with our previous comments to FDA,[26] that FDA should clarify its interpretation of the statutory patent listing requirement as applied to NDA-approved drug-device combination products (including the device constituents and components thereof) and associated digital applications, among other things. But it should not add new limitations that make patent listing more restrictive.

II. Specific Questions (Subsections B-E of Federal Register Notice)

B. Drug Product Patents

1. Are there elements of FDA's regulatory definition of drug product or dosage form in § 314.3(b) that may be helpful to clarify to assist NDA holders in determining whether a patent claims the finished dosage form of an approved drug product?

2. What factors should FDA consider in providing any clarifications related to whether device-related patents need to be submitted for listing as a patent that claims the drug? For example, what are the advantages and disadvantages of requiring patents that claim a device constituent part of a combination product approved under section 505 of the FD&C Act to also claim and/or disclose the active ingredient or formulation of the approved drug product (or the drug product class) to fall within the type of patent information that is required to be submitted to FDA for listing in the Orange Book? Also, how, if at all, should this analysis be affected by considerations about whether the device or specific component of device claimed in the patent is "integral" (see 68 FR 36676 at 36680) to the administration of the drug?

In responding to the above questions, PhRMA focuses on single-entity drug-device combination products.[27] In this context, PhRMA recommends that FDA confirm that patents claiming the device constituent of an NDA-approved drug-device combination product or a component thereof—including patents that do not disclose or claim the active ingredient or formulation of the approved drug product—meet the listing standard. That is, these patents claim the drug for which the applicant submitted the NDA and therefore must be listed if they

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[26] *See* PhRMA, Comments to Docket No. FDA-2011-N-0830 (June 8, 2015), at 8 ("PhRMA urges FDA to clarify its stance on the listability of patents covering device constituents of NDA-approved drug-device combination products . . . .").

[27] 21 C.F.R. § 3.2(e)(1). We do not address co-packaged or cross-labeled combination products in these comments.

could reasonably be asserted upon an unlicensed person engaging in the manufacture, use, or sale of the drug.

Listing patents claiming the device constituent of an NDA-approved drug-device combination product or a component thereof aligns with the statute, regulations, and FDA's longstanding view that a patent need not claim all aspects of a finished drug product in order to be required to be listed. It also advances the objectives of the Hatch-Waxman Amendments by providing notice, an incentive for patent challenge, and an opportunity for all parties to reach early resolution of patent issues. Further, listing these patents is consistent with the significant innovation and patient benefit brought by novel delivery devices and recognizes the costs and burdens of developing and obtaining approval of such devices in connection with an NDA. Although we believe that listing these patents is fully consistent with existing law, FDA's failure to explicitly confirm its agreement with this interpretation has led to uncertainty that has persisted for over 15 years.[28] FDA should now take this opportunity to expressly confirm that these patents are required to be listed if they could reasonably be asserted upon an unlicensed person engaging in the manufacture, use, or sale of the drug. FDA need not amend any regulatory definitions to provide this confirmation. To the extent FDA decides to nevertheless impose any novel restriction on listing these patents notwithstanding the above, FDA should implement any such restriction on a prospective basis only, given longstanding practice in the industry of submitting information regarding such patents for inclusion in the Orange Book and in light of the fact that FDA has not substantively responded to requests for confirmation.

a) Patents that claim the device constituent of an NDA-approved drug-device combination product or a component thereof are drug product patents subject to the listing requirements, and listing these patents advances the objectives of Hatch-Waxman.

The FDCA requires that NDA applicants and holders submit for publication in the Orange Book information regarding "any patent which claims the drug for which the applicant submitted the application . . . and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug."[29] Similarly, FDA's regulations require an applicant to submit for listing in the Orange Book "each patent that claims 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 if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product."[30]

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[28] *See* PhRMA, Comments to Docket No. FDA-2011-N-0830 (June 8, 2015), at 8 (describing the "lingering uncertainty" associated with FDA's position on the listability of patents covering device constituents of NDA-approved drug-device combination products).

[29] *See* FDCA §§ 505(b)(1), 505(c)(2).

[30] 21 C.F.R. § 314.53(b)(1).

FDA has long interpreted "drug" in the patent listing provisions to mean the approved drug product.[31] Moreover, FDA's established practice indicates that a patent need not claim all aspects of the NDA-approved drug product to meet the listing standard. This practice is consistent with the FDCA since it is not necessary to claim all aspects of the NDA-approved drug product in order to reasonably assert a claim of patent infringement for that drug product. The regulations recognize that listable patents "consist of drug substance (active ingredient) patents,"—i.e., those covering the active substance, itself a component of the approved drug product—as well as "drug product (formulation and composition) patents."[32] In contrast, FDA clarified that patents on packaging and containers are ordinarily not listable, reasoning that "packaging and containers are distinct from the drug product and thus fall outside of the requirements for patent submission."[33]

As FDA explained in the preamble to a 2003 final rule on patent listing, however, "[t]he key factor [in determining whether a patent on a device or container is listable] is whether the patent being submitted claims the finished dosage form of the approved drug product."[34] FDA's regulations define "drug product" as "a finished dosage form, e.g., tablet, capsule, or solution, that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients."[35] A dosage form is "the physical manifestation containing the active and inactive ingredients that delivers a dose of the drug product[,]" which includes "such factors as: (1) [t]he physical appearance of the drug product; (2) [t]he physical form of the drug product prior to dispensing to the patient; (3) [t]he way the product is administered; and (4) [t]he design features that affect frequency of dosing."[36] FDA has confirmed that dosage forms include metered aerosols, metered sprays, and pre-filled drug delivery systems.[37] FDA also has stated that device constituents of NDA-approved combination products and components thereof are part of a drug product.[38]

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[31] *See* 67 Fed. Reg. 65,448, 65,449 (Oct. 24, 2002).

[32] *Id.*

[33] 68 Fed. Reg. 36,676, 36,680 (June 18, 2003).

[34] *Id.*

[35] 21 C.F.R. § 314.3(b).

[36] *Id.*

[37] 68 Fed. Reg. at 36,680.

[38] *See* FDA, Draft Guidance for Industry: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action, at lines 206-09 (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 consist of the formulation, container, pump, actuator, protection cap, and protective packaging, which together constitute the drug product."); FDA, Draft Guidance for Industry: Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products, at lines 1921-24 (Nov. 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"); *see also* FDA, Revised Draft Guidance for Industry: Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI)

Because the device constituents of an NDA-approved drug-device combination product and components thereof are part of the finished dosage form (and, therefore, the drug product), patents that claim these devices and components are drug product patents that must be listed if they meet the other conditions of the statutory listing standard. Even where such a patent does not claim and/or disclose the active ingredient or formulation, the patent still claims the drug product approved in the NDA. Indeed, FDA's regulations provide that, if a patent meets the requirements for listing because it claims the drug product, "the applicant is not required to provide the information . . . on whether that patent also claims the drug substance."[39] It is appropriate to consider these device-related patents to be drug product patents even when they do not disclose or claim the active ingredient or formulation, given that it often is impossible to separate the device constituents of an NDA-approved, single-entity, drug-device combination product from the rest of the drug product and be left with a functioning product that can achieve its intended use. In fact, the devices might only be authorized for marketing by virtue of their approval as part of a drug product in the NDA and might not have separate authorization for marketing as a device. Accordingly, PhRMA urges FDA to expressly confirm that these patents must be submitted for listing, provided that they meet the other conditions of the listing standard, regardless of whether the patent claims and/or discloses the active ingredient or formulation of the approved drug product.

This conclusion is appropriate based on an application of traditional patent law principles regarding the meaning of "claim." The ordinary conception of a patent "claim" should govern how to determine whether a patent claims an approved drug product, including its constituent and component parts,[40] particularly because FDA has described its role in the Orange Book listing process as "ministerial."[41] For example, a patent claim using the transitional phrase "comprising" need not identify a drug product by name or otherwise mention the drug product in order for the patent's claims to cover that drug product. Instead, "'comprising' is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim."[42] In other words, a drug product falls within the literal scope of a patent claim that uses the "comprising" transitional phrase and reads on a device component present in a finished NDA-approved drug product. Further, the Federal Circuit has explained that "a patent must be

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Products - Quality Considerations (Apr. 2018) (describing device components such as the actuator as part of the device constituent part of a drug-device combination product).

[39] 21 C.F.R. § 314.53(c)(2)(S)(2).

[40] 67 Fed. Reg. at 65451 (citing *Hoechst-Roussel Pharms. v. Lehman*, 109 F.3d 756, 760 (Fed. Cir. 1997)) (explaining that the Federal Circuit "considered the meaning of the term 'claim,' and the term's relationship to the concept of infringement, and noting that "[t]he court's reasoning and conclusion are equally applicable to patent listings"); *Hoechst-Roussel*, 109 F.3d. at 760 ("Congress deliberately chose the term 'claims' because it already had a well-known meaning and usage in the patent law.").

[41] *See, e.g.*, 68 Fed. Reg. at 36,683 ("Indeed, the requirement of prompt publication ('upon submission'), combined with the 30-day timeframe for updating the Orange Book, are strong evidence that Congress did not intend us to undertake anything other than a ministerial action.").

[42] *See*, *e.g.*, *Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 501 (Fed. Cir. 1997); *see also* U.S. PTO, Manual of Patent Examining Procedure, § 2111.03 (9th ed., rev. Oct. 2019).

listed if it contains a product claim that reads on the drug that is the subject of the NDA . . . . The listing decision thus requires what amounts to a finding of [literal] patent infringement."[43] A claim is literally infringed if "each of the claim limitations 'reads on,' or in other words is found in, the accused" product.[44] An accused product containing a claimed device or device component in the NDA-approved product would literally infringe the patent—and the patent is therefore appropriately listed—*even if* the patent does not specify the particular drug product or active ingredient covered by the NDA.

Confirming that patents claiming a device constituent of an NDA-approved drug-device combination product or a component thereof are required to be listed aligns with other aspects of the statute and regulations and past agency practice. It is clear from FDA's regulations that a patent need not claim the entire approved drug product to be required to be listed. Indeed, patents covering only the drug substance—i.e., one component of the drug product—must be listed as a "patent which claims the drug." Similarly, a method-of-use patent does not need to claim all approved uses of a drug—or even completely cover one approved method of use—in order to be required to be listed.[45] In explaining that patents claiming intermediates are not listable, FDA emphasized that intermediates "are not present in the finished drug product" and distinguished them from "drug substances or *components in the finished drug product*."[46] And FDA has found that release mechanisms of extended-release drugs are part of the composition or formulation of the drug,[47] meaning patents on these mechanisms would claim the drug and are required to be listed if they could reasonably be asserted upon an unlicensed person engaging in the manufacture, use, or sale of the drug. To consistently read the word "drug" in the statute, FDA also should not require that a patent claim the entire finished drug product of an NDA-approved drug-device combination product to be listed; indeed, it is not necessary to claim all aspects of the NDA-approved drug product in order to reasonably assert a claim of patent infringement for that finished drug product. Patents claiming different components of the finished drug product—whether the component is the drug substance or some or all of a device constituent subject to the NDA—should be listed.[48]

Listing patents on device constituents of an NDA-approved drug-device combination product and components thereof also best squares with the statutory language requiring listing

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[43] *Apotex, Inc. v. Thompson*, 347 F.3d 1335, 1344 (Fed. Cir. 2003); *see also Hoechst-Roussel*, 109 F.3d at 759-760.

[44] *Allen Eng'g Corp. v. Bartell Indus., Inc.*, 299 F.3d 1336, 1345 (Fed. Cir. 2002) (quoting *Baxter Healthcare Corp. v. Spectramed, Inc.*, 49 F.3d 1575, 1583 (Fed. Cir. 1995); *Amhil Enters. Ltd. v. Wawa, Inc.*, 81 F.3d 1554, 1562 (Fed. Cir. 1996)).

[45] 21 C.F.R. § 314.53(b)(1).

[46] 68 Fed. Reg. at 36,680 (emphasis added).

[47] *See* FDA Response to Citizen Petitions, Docket Nos. 2004P-0506/CP1, 2004P-0472/CP1 & SUP1, 2004P-0540/CP1, and 2004P-0340/CP1 (Jan. 28, 2005), at 4.

[48] This approach also accords with section 201 of the FDCA, which defines "drug" to include components of a drug. *See* FDCA § 201(g)(1) (defining "drug" to include "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals," and "articles intended for use as a component of any article specified" in the previous clause).

of "any patent which claims the drug *for which the applicant submitted the application*." For this type of combination product, the device constituent or component is marketed pursuant to the combination product NDA. Many delivery devices are not separately cleared or approved by FDA, so the only legal basis for marketing them is the fact that they were approved as part of a drug product in an NDA. And although device constituents are sometimes referred to as part of a "container closure," this does not make them mere "containers" for patent listing purposes; FDA's regulations recognize that container closures may be part of the drug product.[49] Indeed, FDA considers device constituents in determining whether a generic drug-device combination product and its reference listed drug are therapeutically equivalent *drug products*.[50]

In particular, patents claiming the device constituents of an NDA-approved drug-device combination product or components thereof are required to be listed where they are integral to the drug product, as reasonably determined by the NDA holder; however, FDA need not conclude that a device or component is integral to conclude that patents claiming it are required to be listed. Integral devices or integral device components include those that contribute to safe and effective drug administration and/or delivery and include (among others) devices such as dose-counter devices, pre-filled injection devices, and inhalers that control the delivery of the drug formulation, and components thereof such as pen injector drive mechanisms.[51] For these devices and their components, separating the patented device or device component from the drug product while maintaining the drug product's function—and its safety and efficacy—would be difficult if not impossible. Nevertheless, because "integral" is a subjective term and FDA's patent listing responsibilities are ministerial in nature, we do not recommend adopting a patent listing standard in which listability turns on whether a device constituent or component is "integral." To the extent that FDA decides otherwise, FDA should, at a minimum, recognize that the device constituents of single-entity drug-device combination products and components thereof are "integral" to the administration of the drug.

Finally, listing patents claiming device constituents of an NDA-approved drug-device combination product and components thereof in the Orange Book advances the objectives of Hatch-Waxman because it serves an important notice function. If FDA were to limit the types of

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[49] *See*, *e.g.*, 21 C.F.R. § 314.50(d)(1)(ii)(*a*) (referring to submission of information on "specifications necessary to ensure the identity, strength, quality, purity, potency, and bioavailability of the *drug product*, including, for example, tests, analytical procedures, and acceptance criteria relating to sterility, dissolution rate, container closure systems . . ." (emphasis added)).

[50] *See* FDA, Response to Citizen Petition of King Pharms., Docket Nos. FDA-2007-P-0128 and FDA-2009-P-0040 (2009), at 7 ("FDA considers the auto-injector constituent part along with the drug constituent part when determining therapeutic equivalence ratings for a drug/auto-injector combination product"); 21 C.F.R. § 314.3(b) ("*Therapeutic equivalents* are approved *drug products* that are pharmaceutical equivalents for which bioequivalence has been demonstrated, and that can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling." (second emphasis added)).

[51] For instance, in discussing inhalation sprays, FDA has explained that "[t]he dose is delivered by the integral pump components of the container closure system to the lungs by oral inhalation for local and/or systemic effects. The container closure system of these drug products consists of the container, closure, and pump, and can also include protective packaging." *See* FDA, Guidance for Industry: Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation, at 4 (July 2002).

device patents that could be listed in the Orange Book, generic applicants might fail to identify drug-product patents that are not listed, thereby increasing the risks of infringing such patents upon entering the market and being subject to an injunction and/or potential damages. It might prove especially difficult to identify patents that do not disclose or claim the active ingredient or formulation of the approved drug product but nevertheless claim the drug product and would be infringed by a generic drug-device combination product. As discussed further in section I, listing these patents also facilitates early resolution of patent disputes concerning them and provides an opportunity for 180-day exclusivity for generic first applicants, which incentivizes generic entry.

b) FDA should expressly confirm that patents claiming device constituents of an NDA-approved drug-device combination product and components thereof are required to be listed, and any change to that policy should be prospective only.

For the above reasons, PhRMA recommends that the agency expressly confirm that NDA applicants and holders must list patents claiming the device constituent of an NDA-approved drug-device combination product or a component thereof as drug product patents, if the patent could reasonably be asserted if an unlicensed person engaged in the manufacture, use, or sale of the drug. Although FDA could amend its regulatory definition of drug product or dosage form to clarify that such patents are required to be listed, it need not do so to provide this confirmation.

In any case, if FDA nevertheless decides to adopt a new policy restricting the listing of patents claiming a device constituent of an NDA-approved drug-device combination product or a component thereof, FDA should implement any such new policy on a prospective basis only, consistent with prior practice. Recognizing the fairness concerns with retrospective application of a new patent listing policy, FDA applied prospectively the 2003 final rule requiring listing of patents that claim different polymorphs of the active ingredient in certain circumstances.[52] FDA acknowledged "legitimate confusion" regarding its prior position on listing of such patents, as well as uncertainty resulting from court decisions and public statements.[53] Just as with polymorph patents, FDA's position as to the listing status of patents covering device constituents of NDA-approved drug-device combination products and their components would benefit from clarification. Over the past 15 years, industry has repeatedly sought clarification from FDA about which device-related patents should be listed.[54] This issue also has been the

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[52] 68 Fed. Reg. at 36,696.

[53] *Id.* at 36,678.

[54] *See* Novo Nordisk Inc., Request for Advisory Opinion, Docket No. FDA-20 12-A-1169 (Nov. 26, 2012); 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. 2007 A-0261 (June 21, 2007); Ropes & Gray LLP on behalf of AstraZeneca, Request for Advisory Opinion Concerning "Orange Book" Listing of Patents, Docket No. 2006A-0318 (Aug. 10,

source of litigation.[55] Given this uncertainty, FDA ought to apply any policy change with regard to patent listing prospectively, as it has in the past.

As with polymorph patents, a prospective policy would avoid "upsetting legitimate expectations held by those who had relied on [the agency's] earlier interpretation of the act."[56] In the vacuum created by the lack of FDA guidance and in light of the legal and policy considerations described above, listing patents covering device constituents of drug-device combination products and their components has become industry practice, as evidenced by the various requests for advisory opinions submitted by industry, which notified FDA that innovators would be submitting such patents for listing in the Orange Book.[57] FDA subsequently listed these device patents in the Orange Book and, to our knowledge, did not notify applicants that the submitted patents were not eligible for listing per 21 C.F.R. § 314.53(c)(2)(ii).[58] An FDA decision to prevent listing of such device patents would thus upset industry practice and legitimate expectations, which are based reasonably on the statutory language, the regulatory language and FDA's statements thereon, policy considerations, and FDA's practice of listing the relevant patents for more than a decade.

Finally, FDA has explained that "a statutory grant of legislative rulemaking does not encompass the power to implement . . . regulations on a retroactive basis in the absence of express language granting such power," which does not exist here.[59] Moreover, the retroactive application of a new policy could disrupt pending litigation (e.g., patent litigation based on previously listed patents) and invite additional litigation (e.g., antitrust lawsuits against innovators, even though patent listing was reasonable and consistent with the statute and industry practice). Furthermore, retroactive application of new policy could call into question the first-applicant status of generic filers who challenged a previously listed patent, contrary to current FDA policy.[60] Given the absence of express language authorizing retroactive application

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2006); GlaxoSmithKline, Request for Advisory Opinion Concerning "*Orange Book*" Listing of Patents, Docket No. 2005A-0015 (Jan. 10, 2005).

[55] *See King Pharms., Inc. v. Intelliject, Inc.,* No. 1:11-cv-00065-UNA (D. Del. filed 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. *See also In re Lantus Direct Purchaser Antitrust Litig*., 950 F.3d 1 (1st Cir. 2020) (class action alleging improper listing of device patent in Orange Book). Innovators also have faced lawsuits for *not* listing patents in the Orange Book. *See* Complaint, *Mut. Pharm. Co. v. Hoechst Marion Roussel, Inc*., No. 96-cv-1409, 1996 WL 34406666 (E.D. Pa. Feb. 23, 1996) ("Had the '129 patent been listed in the Orange Book, [the plaintiff] would not have expended over $500,000.00 to develop its generic . . . product . . . .").

[56] 68 Fed. Reg. at 36,696 (citing 67 Fed. Reg. at 65,457).

[57] *See* Forest Labs. Advisory Opinion Request, *supra* note 54, at 5.

[58] *See id*.

[59] 68 Fed. Reg. at 36,696 (citing *Bowen v. Georgetown Univ. Hosp*., 488 U.S. 204, 208–09 (1988)).

[60] *See* 21 C.F.R. § 314.94(a)(12)(viii)(B) ("If the list reflects that an NDA holder has requested that a patent or patent information be removed from the list and one or more first applicants are eligible for 180-day

and the deleterious effects of any such application, FDA should apply a patent listing policy change only prospectively.

C. Method-of-Use Patents

1. What information should FDA consider regarding when a patent that claims a method of using a device constituent part, or only a component of a device constituent part, might or might not meet the statutory standard for submission by the NDA holder for listing in the Orange Book as a method-of-use patent? Should FDA consider whether: (1) The patent claims and/or discloses the active ingredient or formulation of the approved drug product (or the drug product class)?; (2) the device constituent part is described in certain sections of the listed drug labeling?; or (3) use of the device is described in labeling for the listed drug, but the device is not a constituent part of the drug product? Should FDA consider whether the drug product labeling states that the drug is only for use with the specific device? Should FDA also consider device labeling, for example whether the device labeling indicates the device is for use with the specific drug?

The FDCA requires NDA applicants and holders to submit for publication in the Orange Book information regarding any patent "which claims a method of using [the] drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug."[61] FDA regulations similarly require submission of information for each patent that claims "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 if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product."[62] As explained in Section B.2, "drug" encompasses the approved drug product, including the device constituents of an NDA-approved drug-device combination product and components thereof, and a patent need not claim every single aspect of an approved drug product in order to fall within the listing requirement.

Similarly, PhRMA interprets the FDCA and FDA's implementing regulations to require listing of patents claiming a method of using a device constituent or component thereof in an NDA-approved single-entity combination product if the patent could reasonably be asserted upon an unlicensed person engaging in the manufacture, use, or sale of the drug—regardless of

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exclusivity based on a paragraph IV certification to that patent, the patent will remain listed until any 180-day exclusivity based on that patent has expired or has been extinguished."); FDA, Guidance for Industry: 180-Day Exclusivity: Questions and Answers, at lines 626-28 (Jan. 2017) ("FDA will not remove a patent from the Orange Book if the removal would deprive a first applicant of 180-day exclusivity to which it is otherwise entitled.").

[61] FDCA §§ 505(b)(1), 505(c)(2).

[62] 21 C.F.R. § 314.53(b)(1).

whether the patent claims and/or discloses the active ingredient or formulation of the approved drug product (or the drug product class).[63]

2. What information should FDA consider regarding whether there are circumstances in which a patent claiming the way an approved drug product is administered would meet the statutory standard for submission by the NDA holder for listing in the Orange Book as a drug product patent rather than a method-of-use patent?

Given FDA's ministerial role as to patent listing matters, it is neither necessary nor appropriate for FDA to substantively evaluate whether a patent contains drug product claims or method-of-use claims.[64] FDA should be guided by how an applicant characterizes the patent in its Form FDA 3542 in determining whether a patent claiming the way an approved drug product is administered would qualify as a drug-product patent rather than a method-of-use patent. If the Form FDA 3542 indicates that the patent claims one or more approved methods of using the drug product, the patent would qualify as a method-of-use patent. If instead the Form FDA 3542 indicates that the patent claims an active ingredient or the approved drug product, the patent would qualify as a drug substance or a drug product patent, respectively.[65] Deferring to applicants' characterizations of patents is consistent with FDA's ministerial role in Orange Book patent listing and recognizes that FDA's expertise is in approving and regulating safe and effective drugs, not patent matters.

3. What information should FDA consider regarding whether there are circumstances in which a method-of-use patent claiming the way an approved drug product is administered that is not described in FDA-approved product labeling would meet the statutory standard for listing in the Orange Book?

As noted earlier, given FDA's ministerial role as to patent listing matters, the NDA applicant, not FDA, must assess whether a method-of-use patent claiming the way an approved drug product is administered that is not described in FDA-approved product labeling would meet the statutory standard for listing in the Orange Book. According to 21 C.F.R. 314.53(b)(1), "[f]or patents that claim a method of use, the applicant must submit information only on those patents that claim indications or other conditions of use for which approval is sought or has been granted in the NDA."

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[63] Again, we do not address co-packaged or cross-labeled combination products in these comments.

[64] *Apotex, Inc. v. Thompson*, 347 F.3d at 1347, 1349 (agreeing with government appellees' argument that the FDCA "does not impose any duty on the FDA to review the accuracy of the submitted patent information because it is the NDA holder who files the required patent information, based on a judgment as to whether the patent claims the drug or a method of using the drug that is the subject of the NDA" and stating "[o]nce the NDA holder submits that information to the FDA, the agency's sole responsibility under the statute is to 'publish it.'").

[65] Of course, patents can contain more than one type of claim, so it may not be appropriate in all circumstances to classify a patent only as being a drug substance patent, a drug product patent, or a method-of-use patent.

D. REMS-Related Patents

1. What information should FDA consider regarding whether patents that claim how the sponsor has implemented a particular REMS requirement meet the statutory requirement for the type of patent information that is required to be submitted to FDA for listing in the Orange Book? What factors should be considered in making this determination?

PhRMA believes that patents are not, and should not be, excluded from eligibility for listing in the Orange Book solely on the ground that they relate to a REMS. The statute does not exclude patents otherwise meeting the listing criteria from listing based on the subject matter to which they relate. A REMS patent must be listed if it meets the criteria set forth in the statute and 21 C.F.R. § 314.53—e.g., if it claims an approved method of use of a drug as described by the approved labeling.[66] The statute and regulations thus already identify the factors that govern whether a REMS-related patent must be listed. Indeed, given FDA's ministerial role in patent listing, it would be difficult for the agency to administer an alternative framework in which "REMS patents," however ill-defined, were excluded from listing.

2. Are there other issues related to patents that claim how the sponsor has implemented a particular REMS requirement that FDA should consider with regard to listing patent information in the Orange Book, including any potential impact listing such patents in the Orange Book could have on development of REMS for generic versions of products? For example, does listing patent information in the Orange Book for such patents pose difficulties for ANDA applicants in developing a single, shared system REMS for that product?

In light of the recent enactment of the Further Consolidated Appropriations Act, PhRMA believes that any concerns regarding the impact of patent listing on the development of REMS for generic versions of products are unfounded. Single, shared system REMS are no longer generally required under amended section 505-1(i) of the FDCA.[67] Where elements to assure safe use (ETASU) are required, an ANDA drug generally may use "a different comparable aspect" of the ETASU rather than a single, shared system with the listed drug.[68] Because a single, shared system REMS is not a blanket requirement, generic companies are free to develop their own REMS with ETASU systems, addressing concerns that negotiation of a single, shared REMS may delay generic approval.

E. Patents for Digital Applications

1. If an approved drug product has an associated digital application (e.g., a mobile application that accepts and records information from an ingestible sensor in a drug product), what factors should be considered in

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[66] *See* 21 C.F.R. § 314.53(b) (authorizing the listing of method-of-use patents "that claim indications or other conditions of use for which approval is sought or has been granted in the NDA").

[67] Further Consolidated Appropriations Act, 2020, Pub. L. No. 116-94, § 610, 133 Stat. 2534, 3136 (2019).

[68] FDCA § 505-1(i)(1)(C)(i).

determining whether a patent that claims an aspect of that digital application meets the standards for listing in the Orange Book?

2. Are there other issues related to patents for digital applications associated with approved drugs that should be considered with regard to listing patent information in the Orange Book?

Given the nascency of digital health technologies and the need to resolve important regulatory issues, FDA's questions in subsection E of the Federal Register notice cannot be answered fully at this time.

As FDA is aware, the future of the burgeoning digital health sector remains uncertain. While the coming years will likely see substantial advancements in digital health, it is unclear exactly what shape those advancements will take. Because of this uncertainty, it is not possible to identify all of the factors and issues the agency should consider when determining whether patents on digital applications should be listed in the Orange Book.

Further, critical questions regarding FDA's treatment of digital applications remain under consideration. Indeed, PhRMA raised several relevant issues in comments on FDA's proposed framework for Prescription Drug-Use-Related Software ("PDURS"),[69] and FDA has not yet issued draft or final guidance on these issues. For instance, in the PDURS docket, PhRMA urged FDA to clarify when it will treat a drug and digital application as a combination product.[70] While FDA acknowledged that PDURS and the corresponding drug could constitute a combination product, more clarity is needed on when FDA will regard drug-software pairings as meeting, and not meeting, the definition of a combination product.[71] There is also uncertainty about when a digital technology—whether a "device" or not—will be discussed by name in drug labeling. PhRMA has articulated concerns with FDA's proposed high bar for adding information about PDURS outcomes to FDA-required labeling and encouraged FDA to adopt a more flexible approach that enables sponsors to add software output to drug labeling.[72] Until FDA adopts a formal regulatory position on these issues, consideration of patent listing policy issues is premature.

Despite this uncertainty, however, FDA should at least confirm at this time that patents claiming a digital application must be listed in the Orange Book where the digital application is approved as part of a combination product with the drug under an NDA and/or where software is referenced by name in drug labeling.

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[69] PhRMA, Comments to Docket No. FDA-2018-N-3017 (Jan. 22, 2019).

[70] *Id.* at 16–17.

[71] *Id.*

[72] *Id.* at 13–16.

III. Conclusion

PhRMA appreciates FDA's consideration of these comments. We look forward to a continued dialogue with the agency and other stakeholders on these issues.

Respectfully submitted,

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