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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:

Sanofi is an integrated, global healthcare leader focused on the discovery, development, and distribution of prescription therapies and consumer products, including innovative drugs and human vaccines. Sanofi appreciates the opportunity to provide these comments to the above-referenced docket.

In the *Federal Register* notice announcing the opening of this docket, the U.S. Food and Drug Administration (FDA or the Agency) requested comment on several questions relating to the submission of patent information under section 505 of the Federal Food, Drug, and Cosmetic Act (FDCA) and the listing of such patent information in the Orange Book.[1] This comment addresses several of these questions identified below. Specifically, this comment responds to FDA's questions about whether patent listing requirements should be clarified, drug product patent listing, method-of-use patent listing, and the advantages of patent listing.

Sanofi has a particular interest in the Agency's request for comments regarding the patent listing requirement because Sanofi currently is defending itself against an antitrust class action relating to the patent listing for the Lantus® SoloSTAR®, a drug-device combination product in the form of a pre-filled insulin glargine injector pen. The complaint, brought by corporate drug wholesalers, alleges that Sanofi improperly delayed competition for Lantus® SoloSTAR® by submitting patent information concerning the device for listing in the Orange Book.[2]

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[1] FDA, *Listing of Patent Information in the Orange Book; Establishment of a Public Docket; Request for Comments*, 85 Fed. Reg. 33,169, 33,173 (June 1, 2020).

[2] Second Amended Class Action Complaint & Demand for Jury Trial, *In re Lantus Direct Purchaser Antitrust Litig.*, No. 16-CV-12652-JGD (D. Mass. Feb. 20, 2018), ECF No. 51.

The United States District Court for the District of Massachusetts twice dismissed the case, finding that it was reasonable for Sanofi to submit information to FDA regarding U.S. Patent No. 8,556,864 (the '864 patent). The '864 patent claims the SoloSTAR® drive mechanism, which has a dose dial sleeve and dose limiting mechanism that allow the user to set, and the device to consistently and accurately deliver, a safe and effective dose of the insulin glargine contained in the pre-filled drug delivery system. The court held that "[t]he '864 Patent indisputably claims components of the Lantus SoloSTAR, which . . . Sanofi correctly had reason to believe met the definition of 'drug product' under the ambiguous FDA guidance."[3] Moreover, the court based its conclusion on "confusion in the industry" about that guidance, which described what patents for pre-filled drug delivery systems must expressly set forth in the claims in order to be subject to the patent listing requirement, as evidenced by requests for clarification from numerous innovative drug companies raising "the very question" presented in the litigation (and one of the questions posed by FDA for comments to this docket).[4] The district court found that the "letters, posing the question of whether component patents must be listed, further show what this court has held—that the ambiguous listing requirements in this area allow for Sanofi's interpretation permitting the listing of the '864 Patent." So holding, the district court rejected the drug wholesalers' argument that the SoloSTAR® device was mere "packaging" and that patents claiming part or all of the device were not properly submitted to FDA for listing in the Orange Book.[5]

On appeal, the United States Court of Appeals for the First Circuit held that Sanofi improperly submitted the '864 patent to FDA for listing in the Orange Book.[6] The First Circuit gave little weight to the record of FDA's evaluation and approval of the new drug application (NDA) supplement for the Lantus® SoloSTAR® and determined—incorrectly—that the patent does not claim any injector pen and thus did not—in the court's view—"claim" the drug product.[7] The First Circuit also held that Sanofi could defend itself against antitrust liability if it could show that its interpretation of the patent listing requirements "was the result of a reasonable, good-faith attempt to comply with the Hatch-Waxman scheme."[8] The panel sent the case back to the District of Massachusetts for

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[3] *In re Lantus Direct Purchaser Antitrust Litig.*, No. 16-CV 12652-JGD, 2018 WL 6629708, at *7 (D. Mass. Oct. 24, 2018). The "guidance" to which the court refers appears in the preamble to FDA's 2003 final rule on patent listing issues. *See* FDA, *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 New Drug is Invalid or Will Not Be Infringed*, 68 Fed. Reg. 36,676, 36,680 (June 18, 2003).

[4] *In re Lantus Direct Purchaser Antitrust Litig.*, 2018 WL 6629708 at *8 (citing Letter from GSK to FDA, Docket No. FDA-2005-A-0476 (Feb. 11, 2009); Interim Response to Forest Labs., Inc., Docket No. FDA-2011-A-0363 (Nov. 7, 2011)).

[5] *In re Lantus Direct Purchaser Antitrust Litig.*, 2018 WL 6629708 at *6.

[6] *In re Lantus Direct Purchaser Antitrust Litig.*, 950 F.3d 1, 8 (1st Cir. 2020).

[7] *See id.*

[8] *Id.* at 14.

further proceedings, and the parties currently are engaged in extensive discovery in advance of a trial scheduled for April 2022.

Sanofi believes that the statute and FDA's regulations always have required the listing of patents directed to pre-filled drug delivery devices approved in an NDA and components of such devices, regardless whether such patents (or patents claiming a method of using such a drug delivery device or component) recite or disclose the active ingredient, formulation, or finished dosage form of the approved drug product. Nonetheless, we ask that FDA clarify this point as the Agency addresses the issues described in the *Federal Register* notice. This interpretation is consistent with the language of the statute and the regulations and would advance the purposes of the Drug Price Competition and Patent Term Restoration Act of 1984 (the "Hatch-Waxman Amendments" or "Hatch-Waxman") by ensuring that generic applicants receive notice about patents that might be infringed and enabling efficient resolution of patent litigation. In the event that FDA determines that such patents are not subject to the patent listing requirement, Sanofi asks that FDA implement this limitation with prospective effect only given the long-standing industry practice of submitting such patents for inclusion in the Orange Book based on a reasonable reading of the patent listing requirement and in the absence of any clarification by FDA despite repeated requests by industry over the past fifteen years.

In support of Sanofi's position that the FDCA and FDA's implementing regulations require the submission of information regarding patents directed to pre-filled drug delivery devices approved in an NDA and components of such devices, we respond to several questions posed by FDA. First, Sanofi suggests that FDA provide clarification regarding the extent of the patent listing requirement in light of the reasonable and widespread confusion in the industry (General Question 2). Second, Sanofi responds to FDA's questions regarding drug product patent listing and discusses why patents on NDA-approved pre-filled drug delivery devices and components thereof must be listed (Drug Product Patent Questions 1 and 2). Third, Sanofi responds to FDA's questions regarding method-of-use patent listing and addresses why methods of using NDA-approved pre-filled drug delivery devices and components thereof must be listed (Method-of-Use Patent Question 1). Finally, Sanofi discusses why including patents on drug delivery devices and components thereof in the Orange Book is advantageous for both innovator drug companies and generic or follow-on drug companies and furthers the goals of Hatch-Waxman (General Question 3).

I. Response to General Question 2

> *Question 2*: Given the general increasing complexity of products approved in an NDA (e.g., drug-device combination products, complex delivery systems, associated digital applications), are there any aspects of FDA's interpretation of the statutory requirement for NDA holders to submit information on a patent that claims the drug or a method of using such drug that are not sufficiently clear? If there is a lack of clarity, how could this be resolved?

FDA should confirm the scope of the patent listing requirement with respect to pre-filled drug delivery devices and components thereof.

Sanofi submits this comment because FDA has not yet responded to requests for clarification regarding the scope of the patent listing requirement as it applies to pre-filled drug delivery devices and components thereof. Since 2005, pharmaceutical manufacturers have submitted five requests for advisory opinions asking FDA to clarify its approach to patent listing for drug delivery devices.[9] Collectively, these Requests for Advisory Opinions sought guidance from FDA on, among other things, whether patents directed to drug delivery devices must be listed in the Orange Book if the patents do not claim or disclose the active ingredient or formulation.[10] FDA did not finally respond to these requests until June 1, 2020, the same date on which the Agency published a *Federal Register* notice announcing the opening of this docket. And rather than provide a substantive response to the requests, FDA denied them without comment on their merits and stated that it intends to consider "comments received on the *Federal Register* notice and will not separately address the requests for advisory opinions."[11]

In the absence of guidance from FDA, stakeholders have advanced alternative readings of the patent listing requirement in litigation, including the antitrust class action

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[9] *See* Novo Nordisk Inc., Request for Advisory Opinion, Docket No. FDA-2012-A-1169 (Nov. 26, 2012); Finnegan, Henderson, Farabow, Garrett & Dunner, LLP on behalf of Forest Laboratories, Inc., Request for Advisory Opinion, Docket No. FDA-2011-A-0363 (May 12, 2011); Ropes & Gray LLP on behalf of AstraZeneca, Request for Advisory Opinion, Docket No. FDA-2007-A-0099 (June 21, 2007); Ropes & Gray LLP on behalf of AstraZeneca, Request for Advisory Opinion, Docket No. FDA-2006-A-0063 (Aug. 10, 2006); GlaxoSmithKline, Request for Advisory Opinion, Docket No. FDA-2005-A-0476 (Jan. 10, 2005). We refer to these advisory opinion requests collectively as Requests for Advisory Opinions.

[10] *See* Requests for Advisory Opinions, *supra* note 9.

[11] Letter from Douglas C. Throckmorton & Patrizia Cavazzoni, FDA, to James Ford, GlaxoSmithKline, et al., Docket Nos. FDA-2005-A-0476, FDA-2006-A-0063, FDA-2007-A-0099, FDA-2011-A-0363, and FDA-2012-A-1169, at 9 (June 1, 2020).

relating to the Lantus® SoloSTAR®.[12] These cases highlight the urgent need for regulatory clarity on this topic.

For the reasons set forth below, Sanofi believes that, consistent with the Agency's long-standing requirement that NDA holders submit patents claiming the approved drug product, the patent listing requirement applies—and always has applied—to a patent claiming a pre-filled drug delivery device approved in an NDA or a component of such a device, regardless of whether the patent expressly mentions the active ingredient, formulation, or finished dosage form in the claim or discloses them in the patent. The statutory requirement for patent submission applies if the approved drug product, here a pre-filled drug delivery device, including its components, falls within the literal scope of the patent claim; neither the statute nor regulations limit or excuse that submission based on the level of detail or specificity by which the patent claim encompasses the product.[13] Sanofi asks that FDA confirm this interpretation.

II. Responses to Questions 1 and 2 Regarding Drug Product Patents

> *Question 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?
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> *Question 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

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[12] *See King Pharms., Inc. v. Intellijject, 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). Before the court ruled on this issue, the litigation was dismissed pursuant to the parties' settlement agreement. *See also* note 6, *supra*.

[13] *See Hoechst-Roussel Pharms., Inc. v. Lehmann*, 109 F.3d 756, 760 (Fed. Cir. 1997) ("Congress deliberately chose the term 'claims' because it already had a well-known meaning and usage in the patent law."); FDA, *Applications for FDA Approval to Market a New Drug: Patent 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*, 67 Fed. Reg. 65,448, 65,451 (Oct. 4, 2002) ("The [*Hoechst-Roussel*] court's reasoning and conclusion are equally applicable to patent listings.").

claimed in the patent is "integral" (see 68 FR 36676 at 36680) to the administration of the drug?

FDA should confirm that a patent claiming a pre-filled drug delivery device or a component thereof is subject to the listing requirement, even if the patent does not claim or disclose the active ingredient, formulation, or finished dosage form.

1. FDA has made clear that a patent claiming a pre-filled drug delivery device is a "drug product" patent that is subject to the listing requirement.

For many years, a patent claiming an injector pen such as the pen of the Lantus® SoloSTAR® unquestionably has been subject to the patent listing requirement. Over seventeen years ago, FDA announced that a patent claiming a "pre-filled drug delivery system" is subject to the listing requirement.[14] Pre-filled drug delivery systems include insulin injector pens such as the Lantus® SoloSTAR®, as FDA expressly has recognized.[15]

A patent claiming a pre-filled drug delivery device is within the scope of the statutory requirement to submit for listing information about "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."[16] In regulations, FDA has interpreted this statutory patent listing requirement to encompass "drug substance (active ingredient) patents, drug product (formulation and composition) patents, and method-of-use patents."[17] This approach is consistent with FDA's long-held interpretation of "drug" in this context to mean the approved "drug product."[18]

In 2003, FDA interpreted the statutory and regulatory provisions to mean that a patent that claims a finished dosage form is a drug product patent that is subject to the listing requirement. FDA described this interpretation in rulemaking to promulgate the patent listing regulation. Comments on the proposed rule[19] urged that patents claiming

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[14] 68 Fed. Reg. at 36,680. Our comments are limited to the scope of the patent listing requirement with respect to pre-filled drug delivery devices. We take no position at this time on how the patent listing requirement applies to other drug-device combination products. *See* 21 C.F.R. § 3.2(e).

[15] FDA, *Frequently Asked Questions About Combination Products* (Apr. 9, 2020) (identifying syringes, insulin injector pens, and metered dose inhalers as examples of "prefilled drug delivery systems"), https://www.fda.gov/combination-products/about-combination-products/frequently-asked-questions-about-combination-products#examples.

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

[17] 21 C.F.R. § 314.53(b)(1).

[18] *See* 67 Fed. Reg. at 65,449; *Pfizer, Inc. v. FDA*, 753 F. Supp. 171 (D. Md. 1990).

[19] 67 Fed. Reg. 65,448.

devices or containers that are "integral" to the drug product or require prior FDA approval should be subject to the listing requirement.[20] In response, FDA clarified that 21 C.F.R. § 314.3 supplies the applicable definition of "drug product" for purposes of the regulation requiring the listing of a patent claiming a drug product.[21]

This definition includes a pre-filled drug delivery device. Under the cited definition, "drug product" means "a finished dosage form."[22] "Dosage form," in turn, means "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."[23]

FDA's list of dosage forms includes (among other things) "metered aerosols, capsules, metered sprays, gels, and ***pre-filled drug delivery systems***," as the Agency explained in the preamble to the final rule.[24] FDA distinguished patents relating to these finished dosage forms from patents "for bottles or containers and other packaging," which are not dosage forms and, accordingly, are not subject to the patent listing requirement.[25] A key difference between pre-filled drug delivery systems and packaging is that, unlike packaging, a pre-filled drug delivery device cannot be separated from the drug product without eliminating the drug product's ability to deliver a dose, which is an essential part of the definition of "dosage form."[26]

The category of "pre-filled drug delivery systems" includes insulin injector pens, as FDA expressly has acknowledged.[27] An insulin injector pen therefore is a dosage form (not only as a pre-filled drug delivery system, but also as "the way the product is administered"), and, consequently, a drug product. It follows that a patent claiming an injector pen claims the drug product and, for that reason, is subject to—and always has been subject to—the patent listing requirement.

The approval of a pre-filled drug delivery system in an NDA—that is, as a single entity drug-device combination product with a drug primary mode of action—makes it particularly appropriate to apply the patent listing requirement to patents claiming the

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[20] 68 Fed. Reg. at 36,680.

[21] *Id.*

[22] 21 C.F.R. § 314.3(b).

[23] *Id.*

[24] 68 Fed. Reg. at 36,680 (emphasis added).

[25] *See id.*

[26] *See* 21 C.F.R. § 314.3(b).

[27] *See* note 15, *supra*.

pre-filled drug delivery system. Such a pre-filled drug delivery system is reviewed, approved, and legally marketed based upon its combination with, and its role in administering, the drug constituent part. A patent directed to the pre-filled drug delivery system therefore properly should be subject to the listing requirement as a patent that claims the "drug."

Sanofi asks FDA to confirm that a patent claiming a pre-filled drug delivery system such as an injector pen is subject to the listing requirement, in order to eliminate any dispute about this point.[28]

2. *Patents directed to components of pre-filled drug delivery devices are likewise subject to the patent listing requirement.*

The patent listing requirement applies with equal force to a patent directed to a component of a pre-filled drug delivery device. Such a patent "claims the drug" within the meaning of the statute.[29] We ask that FDA confirm this interpretation, which is appropriate for three reasons.

First, applying the listing requirement to a patent that is directed to a component of the device constituent part of a pre-filled drug delivery device aligns with fundamental principles of patent law. As noted above, in the *Hoechst-Roussel* decision, the Court of Appeals for the Federal Circuit held that Congress used the term "claims" in the Hatch-Waxman Act in its ordinary meaning in the patent law, and the Agency followed the reasoning of that decision in drafting the patent listing regulations in 2002.[30] Under patent law, a patent claims a product if the product falls within the express bounds of the patent claim; that is, if "each of the claim limitations 'reads on,' or in other words is found in," the product.[31] Thus, a patent "claims" a product if each element of the patent claim is found in the product; the fact that the product contains additional elements not specified in the

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[28] Even if FDA changes its interpretation of the patent listing requirement to exclude patents claiming pre-filled drug delivery devices, it was and—until FDA announces such a change—remains reasonable for sponsors to submit information about such patents for listing based upon the statute, FDA's regulations, and the preamble to the 2003 final rule on patent listing issues. *See* page 12, *infra*. The Federal Circuit has made clear that a sponsor is required to list a patent if it reasonably concludes that listing is required, without the need for an analysis of actual infringement. *Bayer Schering Pharma AG v. Lupin, Ltd.*, 676 F.3d 1316, 1325 (Fed. Cir. 2012) (recognizing that section 505(b)(1) "and its implementing regulations encourage broad disclosure and do not require NDA applicants to make an extrajudicial determination of actual infringement.").

[29] *See* FDCA § 505(b)(1).

[30] *See* note 13, *supra*.

[31] *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)).

patent claim does not place it outside the patent's claims.[32] Under well-settled patent law, therefore, a patent on a drive mechanism would cover a pen injector incorporating that drive mechanism, even if that pen injector has additional elements beyond the drive mechanism. Accordingly, the listing requirement applies to a patent directed to a component of the device constituent part of a pre-filled drug delivery device, given that the sponsor reasonably may conclude that the patent "claims the drug" (i.e., the approved pre-filled drug delivery device).

Consistent with this principle of patent law, the patent listing regulation provides that a method-of-use patent is subject to the listing requirement even if it does not claim all of the product's approved conditions of use or any condition of use in its entirety.[33] The regulation appears to recognize that under patent law, a patent may claim a method of using a drug even where the patent is not directed to an entire approved condition of use or all conditions of use of the approved drug product.[34] Similarly, FDA should confirm that a patent directed to a component of a pre-filled drug delivery device also is subject to the patent listing requirement.

Moreover, a patent claim that states that the invention "comprises" specified elements or method steps "does not exclude additional, unrecited elements or method steps."[35] It would be at odds with this principle of patent law for FDA to conclude that a "comprising" claim must recite each and every element of the finished drug product in order

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[32] *See A.B. Dick Co. v. Burroughs Corp.*, 713 F.2d 700, 703 (Fed. Cir. 1983) ("It is fundamental that one cannot avoid infringement merely by adding elements if each element recited in the claims is found in the accused device.") (citing *Temco Elec. Motor Co. v. Apco Mfg. Co.*, 275 U.S. 319, 328 (1928)); *Aspex Eyewear, Inc. v. Altair Eyewear, Inc.*, 818 F. Supp. 2d 348, 363 (D. Mass. 2011), *aff'd*, 484 F. App'x 565 (Fed. Cir. 2012) ("A device is not saved from infringement by adding elements beyond those claimed in a patent; if a claim reads on part of an accused device, then the entire accused device infringes the claim.") (citing *SunTiger, Inc. v. Scientific Research Funding Grp.*, 189 F.3d 1327, 1336 (Fed. Cir. 1999)).

[33] *See* 21 C.F.R. § 314.53(b)(1) ("If the method(s) of use claimed by the patent does not cover an indication or other approved condition of use in its entirety, the applicant must describe only the specific approved method of use claimed by the patent for which a claim of patent infringement could reasonably be asserted . . . .").

[34] *See* 81 Fed. Reg. 69,580, 69,599 (Oct. 6, 2016) (explaining that where the "[p]atented method of use is narrower than an indication or other approved condition of use," the use code "must describe only the specific approved method of use claimed by the patent—not the broader indication or other approved condition of use that may include, but is broader than, the use claimed by the patent.").

[35] *See* United States Patent and Trademark Office, *Manual of Patent Examining Procedure* § 2111.03 (9th ed., rev. 10.2019); *see also Georgia-Pacific Corp. v. United States Gypsum Co.*, 195 F.3d 1322, 1327-28 (Fed. Cir. 1999), *opinion amended on reh'g*, 204 F.3d 1359 (Fed. Cir. 2000); *CIAS, Inc. v. Alliance Gaming Corp.*, 504 F.3d 1356, 1360-61 (Fed. Cir. 2007).

for the patent to be considered to "claim[] the drug" and thus be subject to the listing requirement.

Second, this approach is most consistent with the patent listing regulation, which expressly applies to patents directed to other types of drug product components. For example, a patent directed to the formulation of the drug product is subject to the listing requirement as a "patent that claims the drug"[36] even though it does not necessarily claim or describe all of the drug product's constituents or describe the whole drug product. The same logic compels the listing of a patent directed to a component of the device constituent part of a pre-filled drug delivery device that is approved in an NDA. FDA has described this type of drug-device combination product as a "drug product" and has treated a component of the device as part of that "drug product."[37] Such a component of the device is as much a part of the "drug product" as is the drug constituent part. And just as a patent claiming the drug constituent is subject to the listing requirement,[38] so too should a patent reciting a component of the device constituent part be subject to the listing requirement because that component also is part of the "drug product." Like the drug constituent, a component of the device constituent part may play an essential role in the ability of the drug product to achieve its intended effect; for example, by controlling the dose administered to the patient and the rate of delivering that dose.

Third, this interpretation squares with the definition of "drug" in the FDCA. As noted, the statutory patent listing requirement applies to a "patent which claims the drug . . . or . . . a method of using such drug."[39] Section 201 of the FDCA defines "drug" to include, among other things, "articles intended for use as a component of" a drug.[40] Given that "drug" is defined to include a "component," it is therefore consistent with the statute to interpret the patent listing requirement as including patents claiming components of a "drug" even though the statutory patent listing provision does not refer expressly to

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[36] *See* 21 C.F.R. § 314.53(b)(1).

[37] For instance, FDA has explained that "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, *Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action*, at 6 (Apr. 2003). *See also* FDA, Draft Guidance for Industry, *Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Products—Quality Considerations*, at 29 (Rev. 1, Apr. 2018) (using "drug product" to refer to "the combination product (i.e., the MDI or DPI product) . . . for clarity because pertinent labeling regulations and requirements use the term 'drug product.'").

[38] *See* 21 C.F.R. § 314.53(b)(1) (identifying "formulation" patents as "drug product" patents that must be listed).

[39] FDCA § 505(b)(1).

[40] *Id*. § 201(g)(1).

components. And, because FDA construes "drug" to mean "drug product,"[41] it is also consistent with the statute to interpret the patent listing requirement to apply to patents claiming components of "drug products."

Finally, we address FDA's question as to "how, if at all, should [the patent listing] analysis be affected by considerations about whether the device or specific component of device claimed in the patent is 'integral' to the administration of the drug?"[42] Neither the statute nor FDA's patent listing regulation limits the patent listing requirement to patents directed to "integral" devices or components thereof, nor is it apparent how FDA would define "integral."[43] If FDA nonetheless adopts such a limitation, the Agency should continue to ensure that the listing requirement applies, at a minimum, to patents directed to NDA-approved pre-filled drug delivery devices or components thereof that contribute to the consistent, accurate, safe, and effective administration or delivery of the drug constituent part.

3. *A patent directed to a pre-filled drug delivery device or a component thereof is subject to the listing requirement even if the patent does not claim or disclose the active ingredient, formulation, or finished dosage form.*

The patent listing requirement may apply even if a patent does not expressly recite the active ingredient, formulation, or finished dosage form. Applying patent law principles, no such recitation is needed for a sponsor reasonably to conclude that a patent "claims the drug . . . or . . . a method of using such drug" and that "a claim of patent infringement could reasonably be asserted . . . ."[44] Indeed, a claim may be infringed by an accused product even if the patent does not expressly claim or disclose the active ingredient, formulation, or finished dosage form.[45]

Additionally, a patent directed to a pre-filled drug delivery device or component thereof might not expressly claim or disclose the active ingredient, formulation, or finished dosage form because, for example, the device invention was broader than its application for

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[41] *See* note 18, *supra*.

[42] 85 Fed. Reg. at 33,173 (citing the preamble to the 2003 final rule in which FDA acknowledged, but did not address, the suggestion that "patents claiming devices or containers that are 'integral' to the drug product or require prior FDA approval should be submitted and listed," 68 Fed. Reg. at 36,680).

[43] Nor does the patent law distinguish between "integral" and "non-integral" components in determining whether an accused product falls within a patent claim. *See Abbott Labs. v. Sandoz, Inc.*, 566 F.3d 1282, 1299 (Fed. Cir. 2009) (noting that "*de minimis* infringement can still be infringement") (citing 35 U.S.C. § 271(a); *SunTiger, Inc.*, 189 F.3d at 1336 ("If a claim reads merely on a part of an accused device, that is enough for infringement.")).

[44] FDCA § 505(b)(1).

[45] *See* note 31, *supra*.

delivering a specific active ingredient such that the device developer did not wish to limit the scope of the patent to a specific application, or the drug had not yet been developed. It would be contrary to patent law principles to conclude that the omission of an express limitation somehow causes the patent not to "claim[] the drug."[46] As such, the described patents do claim the drug and they must be submitted to FDA for inclusion in the Orange Book.

Sanofi asks FDA to confirm that, consistent with patent law principles, a patent directed to a component of a pre-filled drug delivery device is subject to the listing requirement even if the patent does not claim or disclose the active ingredient, formulation, or finished dosage form. Alignment with patent law on this point would be appropriate given the "purely ministerial" role that FDA has adopted with respect to patent listing.[47]

Any new limitation on the scope of patents that are subject to the patent listing requirement should have prospective effect only.

1. *Industry practice has been based on a reasonable interpretation of the statute, FDA's regulations, and Agency statements.*

If FDA imposes a new limitation on the types of patents that are subject to the listing requirement, the Agency should do so with prospective effect only. For the reasons discussed above, Sanofi and other sponsors reasonably have understood the patent listing requirement to apply to patents directed to pre-filled drug delivery devices and components of the device constituent part, even if the patent does not recite the active ingredient, formulation, or finished dosage form. Based on this understanding, and in light of FDA's failure to advise otherwise and its self-stated ministerial role in patent listing matters, Sanofi and other sponsors reasonably have submitted such patents for listing in the Orange Book.

The reasonableness of this industry practice is further supported by the absence of any substantive response by FDA to the five Requests for Advisory Opinions on this topic.[48] Additionally, the fact that FDA requested input on these issues through this docket makes clear that the patent listing requirement does not unambiguously exclude from its scope the types of patents addressed in this comment. Given the reasonableness of the existing

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[46] FDCA § 505(b)(1).

[47] *See, e.g.*, *aaiPharma Inc. v. Thompson*, 296 F.3d 227, 237 (4th Cir. 2002) ("The FDA defends this purely ministerial conception of its role in the Orange Book listing process by explaining that it lacks both the resources and the expertise to police the correctness of Orange Book listings."); 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.").

[48] *See* section I, *supra*.

industry practice, it would be appropriate for any policy change that limits the scope of the patent listing requirement to have prospective effect only.

2. *A retroactive limitation on which patents are subject to the patent listing requirement might disrupt pending patent litigation and could lead to additional antitrust litigation.*

If FDA were to limit the scope of the patent listing requirement with retroactive effect, the status of pending Hatch-Waxman patent litigation based on patents that FDA concludes were ineligible for listing would become uncertain. For example, a court might conclude that there no longer is an artificial act of infringement that would support the filing of an infringement claim before the approval of an abbreviated new drug application (ANDA) or section 505(b)(2) application.[49]

Additionally, any determination by FDA suggesting it was unreasonable for sponsors to have interpreted the listing regulations to require the submission of information regarding certain types of patents to FDA for inclusion in the Orange Book could invite additional antitrust lawsuits against sponsors who submitted that information in good faith. Although these types of antitrust claims would lack merit,[50] such cases would consume the resources of the sponsors and the courts. Indeed, Sanofi has endured three years of litigation, two rounds of motion to dismiss briefing before the district court, and one appeal in the antitrust case stemming from the Lantus® SoloSTAR® patent listing. The matter is now in the middle of extensive—and expensive—discovery.

Sanofi asks that FDA apply any limitation on the scope of the patent listing requirement only prospectively because retroactive implementation could lead to disruption of pending patent litigation and the prospect of additional meritless, but resource-intensive, antitrust litigation.

3. *FDA previously applied a new patent listing policy with prospective effect only.*

Applying any change to the patent listing policy only prospectively would be consistent with prior FDA practice. FDA previously declined to apply a change in patent listing policy retroactively in the context of patents claiming polymorphs. In the 2003 final rule, FDA added a requirement that, when submitting information regarding a patent claiming only a polymorph that is the same as the active ingredient described in the NDA

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[49] 35 U.S.C. § 271(e)(2)(A).

[50] The courts have held that an Orange Book listing is "not improper" if the sponsor "had a reasonable basis for the submission." *Organon Inc. v. Mylan Pharms., Inc.*, 293 F. Supp. 2d 453, 460 (D.N.J. 2003). However, the First Circuit recently held that it could not adjudicate whether Sanofi's submission of a patent for listing "was the result of a reasonable, good-faith attempt to comply with the Hatch-Waxman scheme" as a matter of law at the motion to dismiss stage. *In re Lantus Direct Purchaser Litig.*, 950 F.3d at 14.

to FDA for inclusion in the Orange Book, the applicant must certify that it has test data that a drug product containing the polymorph will perform the same as the drug product described in the NDA.[51] FDA acknowledged "legitimate confusion" regarding its prior position on the listing of such patents, as well as uncertainty resulting from court decisions and the Agency's public statements.[52] FDA explained that it would apply the rule only prospectively out of concern for "upsetting legitimate expectations held by those who had relied on [the Agency's] earlier interpretation of the act."[53] Moreover, FDA recognized that "a statutory grant of legislative rulemaking does not encompass the power to implement such regulations on a retroactive basis in the absence of express language granting such power."[54] FDA also delayed the implementation date to allow time for sponsors to collect the data necessary to satisfy the new requirement.[55]

Similar concerns exist here. The requests for advisory opinions and FDA's request for input through this docket reflect "legitimate confusion" regarding the scope of the patent listing requirement in the context of pre-filled drug delivery devices and components thereof. And retroactively applying a new limitation on the scope of patents that are subject to the listing requirement would upset legitimate expectations held by industry. Finally, no express statutory language grants FDA the authority to limit the scope of the patent listing requirement on a retroactive basis. For these reasons, FDA should implement any such limitation with prospective effect only.

III. Response to Question 1 Regarding Method-of-Use Patents

> *Question 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?

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[51] 68 Fed. Reg. at 36,678; 21 C.F.R. § 314.53(b)(1).

[52] 68 Fed. Reg. at 36,678.

[53] *Id.* at 36,696 (citing 67 Fed. Reg. at 65,457).

[54] *Id.* (citing *Bowen v. Georgetown Univ. Hosp.*, 488 U.S. 204, 208-09 (1988)).

[55] *Id.*

A patent claiming a method of using a pre-filled drug delivery device or a component thereof is subject to the patent listing requirement, even if the patent does not claim or disclose the active ingredient, formulation, or finished dosage form.

The analysis set forth above with respect to the patent listing requirement for a patent that "claims the drug" applies equally to the listing requirement for a patent that "claims a method of using such drug."[56] For the same reasons, Sanofi asks FDA to confirm that a patent claiming a method of using a pre-filled drug delivery device or a component thereof is subject to the patent listing requirement, even if the patent does not claim or disclose the active ingredient, formulation, or finished dosage form. An example of such a patent is one that is directed to an approved method of administering the drug by, for example, determining the final dose of a drug contained in a cartridge in a pen-type injector through the configuration or operation of certain device components. Such a patent must be listed in the Orange Book, even if the patent does not claim or disclose the active ingredient, formulation, or finished dosage form.

IV. Response to General Question 3

> *Question 3*: How would NDA holders and prospective 505(b)(2) and ANDA applicants weigh any advantages that may result from listing of additional types or categories of patent in the Orange Book against the potential need to submit additional patent certifications that could result in a delay of approval of a 505(b)(2) application or ANDA?

The listing of patents directed to pre-filled drug delivery devices and components thereof advances the purposes of Hatch-Waxman.

The listing of patents in the Orange Book plays a central role in the Hatch-Waxman system. Two of the purposes of patent listing are particularly relevant here.

First, patent listing provides ANDA and section 505(b)(2) applicants with notice of the drug substance, drug product, and method-of-use patents that claim approved drug products, and thereby aids them in designing their products and preparing to challenge listed patents. This purpose of patent listing is especially important for patents directed to pre-filled drug delivery devices and components thereof. In the absence of Orange Book listing, ANDA and section 505(b)(2) applicants might find it challenging to identify all patents that claim the approved pre-filled drug delivery device and might be infringed by a competing product, particularly where such patents do not claim or disclose the active ingredient, formulation, or finished dosage form. The listing of such patents in the Orange Book promotes competition by helping ANDA and section 505(b)(2) applicants understand

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[56] FDCA § 505(b)(1); *see also* 21 C.F.R. § 314.53(b)(1).

the patent landscape as they develop their products and assess potential intellectual property risks.[57]

Second, patent listing facilitates the efficient resolution of patent disputes before the ANDA or 505(b)(2) product is approved and launched, and before the ANDA or 505(b)(2) applicant faces potential liability for damages. Because the submission of an ANDA or section 505(b)(2) application with a paragraph IV certification is an act of patent infringement,[58] patent disputes based on Orange Book-listed patents can be initiated (and even resolved) before a generic drug or section 505(b)(2) product is approved and launched. ANDA and section 505(b)(2) applicants benefit from the opportunity to obtain certainty regarding the patent landscape for their products without risking exposure to damages for infringement. They would be denied that opportunity if patents directed to pre-filled drug delivery devices and components thereof were not subject to the patent listing requirement. Rather, litigation relating to such patents might not occur until after the approval and launch of the ANDA or section 505(b)(2) product. At that stage, ANDA and section 505(b)(2) applicants would face the risk of a damages award for patent infringement—a prospect that might deter such applicants from seeking approval in the first place—and an injunction. Additionally, a post-launch patent suit would be more complex and resource-intensive given the likelihood that courts and parties also would need to address preliminary injunctive relief and damages.

Finally, we acknowledge that the listing of device-related patents might provide the basis for a 30-month stay of approval of an ANDA or section 505(b)(2) application based upon the timely filing of a patent suit in response to a notification that the applicant has submitted, and FDA has accepted, an ANDA or section 505(b)(2) application with a paragraph IV certification.[59] However, the amendments made in the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 prevent serial 30-month stays that would delay ANDA or section 505(b)(2) approval. Under the current statute, a patent may provide the basis for a 30-month stay only if information about that patent was submitted for listing before submission of the original ANDA or section 505(b)(2) application.[60] Thus, all patents for which information was submitted before submission of the original ANDA or section 505(b)(2) application can support what is, in effect, a single 30-month stay (or, alternatively, separate 30-month stays that all run concurrently). The listing of patents directed to drug delivery devices and components thereof would not be expected to lead to any additional 30-month delay of approval of an ANDA or section 505(b)(2) application beyond the stay that arises from other Orange Book-listed patents. That said, in the

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[57] At least one drug manufacturer has been sued for not listing a patent based on the allegation that the ANDA applicant was deprived of notice of the patent when it developed its product. *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 . . . .").

[58] *See* 35 U.S.C. § 271(e)(2)(A).

[59] *See* FDCA § 505(c)(3)(C), (j)(5)(B)(iii); 21 C.F.R. § 314.52.

[60] *See* FDCA §§ 505(c)(3)(C), (j)(5)(B)(iii).

unlikely case that the listing of patents directed to drug delivery devices and components thereof does form the sole basis for a 30-month stay, the stay would serve the important functions discussed above.

V. Conclusion

Sanofi appreciates the opportunity to comment on these issues and hopes that this input will be useful to FDA. If you have any questions regarding these comments, please contact me at Barry.Sickels@sanofi.com or (908) 981-2531.

Sincerely,

/s/

Barry Sickels
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