Biotechnology Innovation Organization

August 31, 2020

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

Re: Docket No. FDA– 2020–N–1127 (85 Fed. Reg. 33169 (June 1, 2020))
Listing of Patent Information in the Orange Book

The Biotechnology Innovation Organization ("BIO") is submitting these comments in response to the above-referenced Food and Drug Administration ("FDA") *Federal Register* notice requesting comments on listing of patent information in FDA's publication "Approved Drug Products with Therapeutic Equivalence Evaluations" ("Orange Book").[1] BIO commends FDA's efforts to provide additional clarity as to the types of patents subject to listing in the Orange Book, and FDA's acknowledgment that changes to current patent listing practices could have an impact on drug product development. This is an important topic that, in certain respects, could benefit from further guidance and clarity from FDA, and we appreciate the opportunity to comment.

BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial, and environmental biotechnology products.

On behalf of our members, BIO provides the responses that follow to certain of the questions posed by FDA in the June 1 *Federal Register* notice.

BIO Responses to Select "General Questions"

- **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?*

[1] 85 Fed. Reg. 33169 (June 1, 2020).

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FDA is correct in acknowledging the increasing complexity of advanced new drug products that incorporate more innovative technology than in the past. Due to their complexity, such products may present challenges in identifying relevant patents and in demonstrating that a purported generic is the same as the reference drug. This makes the notice function of the Orange Book all the more important as Orange Book patent listings are the vehicle by which prospective 505(b)(2) and abbreviated new drug application ("ANDA") applicants identify patents that claim a particular reference drug. Orange Book listings thus help ANDA and 505(b)(2) applicants to assess the intellectual property landscape related to a reference drug, and to decide on one or more approaches such as different patent certifications, challenging a patent in court, seeking invalidation in one of several available U.S. Patent and Trademark Office proceedings, designing around a patent, filing a suitability petition where appropriate, seeking a label carve out where appropriate, or seeking a license and right of reference or use.

There are aspects of FDA's statutory interpretations regarding the types of patents for complex products that are and are not subject to listing in the Orange Book that we believe would benefit from greater clarity, as detailed in our responses below to other questions posed by FDA. We believe FDA can give full effect to the statutory intent, using its existing authority, without legislative amendment, and without departing from its established ministerial role in administering Orange Book patent listings.

As to how the lack of clarity can be resolved, we believe that guidance documents addressing the questions posed in the *Federal Register* notice would be a valuable step. Additionally, the agency could consider convening periodic public meetings or workshops where stakeholders can discuss patent listing-related topics with the agency. It is our understanding that, over the years, various New Drug Application (NDA) sponsors have made submissions to the agency requesting the agency's opinion regarding whether certain types of device-related patents were subject to listing in the Orange Book. Generally speaking, the agency has not substantively replied to stakeholder requests of that nature, leaving NDA sponsors to make listing decisions without agency feedback. Over time, important recurring questions remained unanswered, creating the potential for judicial decisions that determine the outcomes of these questions from the bench without the benefit of public, stakeholder, or agency input. We believe scheduling periodic public meetings where general patent listing questions can be discussed could be helpful in highlighting how the increasing complexity of NDA-regulated products intersects with Orange Book listing practices. Doing so could not only help FDA shape its current thinking on the topic, but could also provide early indicators of any recurring unanswered questions and legal uncertainty that could be mitigated by agency guidance before systemic problems arise.

- **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?*

As a threshold matter, we ask that the agency clarify what it means by "additional types or categories" of patents. Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act ("FDCA") requires NDA applicants to list two types of patents with FDA: (1) any patent that claims the drug for which the applicant submitted the application, and (2) any patent that claims a method of using such drug if, for either type of patent, 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.[2] While FDA has issued regulations regarding the types of patents that the agency interprets as falling under these categories, FDA's current authorities do not permit the agency to require the listing of additional types of patents beyond those that fall within the scope of the two categories described in the FDCA.

Consequently, BIO interprets FDA's question as an opportunity for clarification on the scope of patents considered to claim an approved drug or a method of using an approved drug, i.e., clarification of those patents that are required to be listed under current law. BIO does not construe FDA's question as the agency seeking to allow the listing of additional types or categories of patents that were not or would not have been subject to the listing requirement in the past.

- ***Question 4:*** *If you think FDA should clarify the type of patents that must be listed in the Orange Book, what factors should FDA consider in implementing this clarification? For example, should FDA consider specific factors in evaluating the timeliness of patent information submitted after such clarification?*

FDA should carefully consider the potential implications of any clarifications from the agency regarding patents that must or must not be listed in the Orange Book. In particular, the agency should not change its position on any types of patents for which the agency previously indicated to industry that the agency viewed the patents as subject to the listing requirement. A move by the agency to narrow its read of patents that must be listed under FDCA § 505(b)(1) would have far-reaching consequences, and would trigger questions about the fairness or legality of such a decision. To the extent that FDA does intend to clarify that certain types of previously listed patents are not subject to the listing requirement, we ask that the agency make a clear statement that the legal requirements for listing such patents in

[2] FDCA § 505(b)(1); 21 U.S.C. § 355(b)(1). *See also* FDCA § 505(c)(2) and 21 U.S.C. § 355(c)(2) for further details on patent listing requirements.

the past were ambiguous, and that past decisions by sponsors to list such patents were not facially unreasonable.

In assessing these issues, FDA should consider whether any clarifications about the types of patents that must and must not be listed should only be applied prospectively. Even if only applied prospectively, the agency should clarify what prospective application entails, including whether there would be listing implications for any previously approved drugs and certification obligations for any pending ANDA or 505(b)(2) applications.

BIO Responses to the "Drug Product Patents" Questions

- **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?*

As noted above, the relevant provision of the FDCA requires listing of "any patent which claims the drug for which the applicant submitted the [NDA…]." FDA's regulatory definition should give the broadest reasonable effect to Congress's intended meaning. FDA should construe "patent which claims the drug" to mean any patent that claims one or more articles used as a component of the drug product, or that claims the composition of the drug product (e.g., a combination of such components or specific amounts, ratios, or configurations thereof). BIO believes that this interpretation comports well with the FDCA § 505(b)(1) requirement that an NDA application include "a full list of the articles used as components" of the drug and a "full statement of the composition" of the drug.[3] We do, however, recommend that FDA clarify its interpretation of its § 314.3(b) "drug product" and "dosage form" definitions as relates to the listing of device patents. We provide our position on this issue in the response to the next question.

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

[3] FDCA § 505(b)(1); 21 U.S.C. § 355(b)(1).

In 21 C.F.R. § 314.3(b), FDA defines "drug product" to mean "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", and defines "dosage form" to mean "the physical manifestation containing the active and inactive ingredients that delivers a dose of the drug product". The "dosage form" definition further specifies that "[t]his includes factors such as: (1) The physical appearance of the drug product; (2) The physical form of the drug product prior to dispensing to the patient; (3) The way the product is administered; and (4) The design features that affect frequency of dosing."

FDA should not construe § 505(b)(1) of the FDCA in a manner that limits listing of patents that claim a device constituent part of a combination product to only those patents that expressly claim or recite a device or device component in combination with the drug's active ingredient or formulation. Interpreting § 505(b)(1) in this way would be taking the concept of "finished dosage form" too far, and would be inconsistent with longstanding patent listing practices not just for drug-device combination products.

This is because the Orange Book listing requirements at 21 C.F.R. § 314.53 have long required the listing of patents that claim "less" than the finished dosage form of approved drugs. For example, there is no dispute that a patent claiming only an active ingredient would be properly listed, even if the finished dosage form is a tablet also containing specific excipients and coatings. Likewise, for a combination drug containing more than one active ingredient, a patent that claims only one active ingredient would be properly listed even if no other active ingredients appear in the patent claims. And the same is true for a patent that claims only the injectable formulation of the active ingredient even if the finished dosage form is a pre-filled syringe having mechanical components that are not mentioned in the patent claims. It is of course correct that a patent that claims a finished dosage form in its entirety should be listed, but it must be understood that patents claiming only ingredients or components of drugs have always been listable. In other words, for a drug patent to claim the entire finished dosage form has been a sufficient but not necessary condition to listing in the Orange Book.

Because it is true that patents have long been subject to the listing requirement even if they claim "less" than the entirety of the drug product, then the same should be true for finished dosage forms that are drug-device combinations, such as metered dose inhalers ("MDI") or pen injectors that are pre-filled, co-packaged or co-labeled for use with specific drug formulations. For example, for MDI drug products, FDA in guidance has explained that the "the formulation, container, valve, the actuator, and any associated accessories (e.g., spacers) or protective packaging collectively constitute the drug product."[4] There is no dispute that a

[4] FDA, *Draft Guidance for Industry: Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products* 60 (1998).

patent claiming only the "formulation" should be listed, even if the patent claims do not also mention a valve, actuator, or other components. What, then, about a patent that claims the MDI's novel valve and actuator assembly but makes no mention of its formulation? Under this FDA guidance, the device assembly with its valve and the actuator is as much a constituent part of the drug product as is the formulation. As such, it would make little sense to require the listing of patents claiming one constituent part of an MDI (the formulation), but bar listing of patents that claim another constituent part of the same MDI (the device assembly with its valve or actuator).

In this way, NDA applicants have reasonably understood prior FDA comments as requiring the listing of patents that claim important components or constituent parts of drug-device combinations, even if these patents claim less than all constituent parts in combination, i.e., less than the entirety of the finished dosage form.[5]

Second, it is not always feasible to draft device patents to include or claim the device in combination with a specific drug active ingredient. For instance, if an NDA sponsor licenses applicator technology for a drug development program from a device partner, that device partner may not want to narrow its patent protection for the applicator which may have multiple applications. This could be true for any number of device technologies developed by third parties from whom NDA sponsors license patents rights. There may also be reasons why a patent cannot claim a device in combination with a specific drug (e.g., if the device

[5] In the preamble to the agency's 2003 rule amending 21 C.F.R. Part 314, the agency provided the following response to comments about listing of patents claiming devices or containers considered integral to the drug product:

> "We agree that patents claiming a package or container must not be submitted. Such packaging and containers are distinct from the drug product and thus fall outside of the requirements for patent submission. However, we have clarified the rule to ensure that if the patent claims the drug product as defined in § 314.3, the patent must be submitted for listing Section 314.3 defines a ''drug product'' as ''* * * a finished dosage form, for example, tablet, capsule, or solution, that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients.'' The appendix in the Orange Book lists current dosage forms for approved drug products. The list includes metered aerosols, capsules, metered sprays, gels, and pre-filled drug delivery systems. The key factor is whether the patent being submitted claims the finished dosage form of the approved drug product. Patents must not be submitted for bottles or containers and other packaging, as these are not ''dosage forms.'' The revised declaration requirements, described in the response to comment 12 in section II.A of this document, detail the information required for submission."

68 Fed. Reg. 36676, 36680 (June 18, 2003).

and the drug were previously patented separately, or if the drug and device are separately disclosed in the prior art already).

Moreover, even if a device patent is written to claim the device in combination with a specific drug, we believe construing § 505(b)(1) to so require would amount to a distinction without meaning. To illustrate this point, imagine a hypothetical where the invention in question is a new and unobvious mechanical component of a drug-delivery device (such that a valid patent claim could be drafted to the component itself). In that scenario, it is normally not difficult from a patentability perspective to write narrower patent claims that claim the component in combination with additional elements, e.g., a delivery device comprising the novel component, or drug-device combination comprising the novel component. Yet, for all practical purposes under the Hatch-Waxman Act, the relevant scope of each such patent is the same because – whether the claims are written one way or the other – each such patent would be infringed by a third party's unauthorized drug-device combination. Moreover, prospective ANDA and 505(b)(2) applicants would derive no additional benefit in the form of advance notice if the relevant patents were written one way or the other. That notice function is served fully by listing the patent in the Orange Book, where the device patent is linked to the reference drug. No additional notice would be accomplished by requiring device patents also to claim the combination with the drug formulation in order to be listed in the Orange Book.

To reiterate, we ask that FDA clarify that a patent that claims a device or device component need not also claim or expressly call out the active ingredient in the drug to be considered a patent that "claims the drug" under FDCA § 505(b)(1). While claiming the drug active ingredient should be sufficient to render a patent that claims a device or device component subject to listing, claiming the active ingredient should not be construed as a necessary factor. Rather, we propose that FDA clarify that, where a patent that claims a device or device component does not claim it in combination with the drug's active ingredient, whether the patent is subject to listing turns on whether the device as used with the drug meets the agency's regulatory definition of a combination product as set forth at 21 C.F.R. § 3.2(e), whether or not specifically designated as such by the agency. If a patent claims a device that is considered a constituent part of a drug-device combination product (or claims a component of such a device), then the patent should be considered one that "claims the drug" for FDCA § 505(b)(1) patent listing purposes.

Thus, under our proposed approach, FDA would clarify that a patent that claims a device or device component is subject to listing if one or more of the following applies:

1) the patent also claims the active ingredient or formulation of the approved drug;
2) the patent claims a device (or component of such a device) that is physically, chemically, or otherwise combined or mixed with a drug and produced as a single entity (applying 21 C.F.R. § 3.2(e)(1);
3) the patent claims a device (or component of such a device) that is packaged together in a single package with a drug or as a unit (applying 21 C.F.R. § 3.2(e)(2)); or
4) the patent claims a device (or component of such a device) that is packaged separately from a drug but that is co-labeled for use with a drug and where both are required to achieve the intended use, indication, or effect (applying 21 C.F.R. § 3.1(e)(3)).

With regard to FDA's request for comments on whether this analysis should be affected by considerations about whether the device or device component claimed in the patent is considered "integral" to administration of the drug, BIO believes the term "integral" as used in the referenced Part 314 preamble is imprecise but, in any case, defining the scope of this term is unnecessary to determine whether a device-related patent must be listed. Under our above proposed approach to clarification of the patent listing requirements, whether a device patent is subject to listing would not require an analysis of whether the device claimed by the patent is "integral" to administration of the drug. Rather, if a device as intended to be used with a particular drug meets FDA's § 3.2(e) definition of a drug-device combination product, then a patent claiming that device should be listed. We believe this approach would be simpler, easier to comply with, and more transparent than a searching inquiry into whether a product feature is integral (as opposed to merely ancillary or peripheral) to the administration of a drug, while at the same time achieving the same objective as FDA's current approach.

Further, as pertains to delivery devices specifically, our proposed approach is consistent with prior FDA guidance that patents claiming a package or container must not be submitted for listing, assuming that the package or container is distinct from the drug product and thus falls outside of the requirements for patent submission. Notably, under our approach, only patents claiming those "containers" that meet the definition of a medical device and are part of a drug-device combination product would be subject to listing. FDA guidance on applicability of cGMPs to combination products indicates that, in the agency's view, in order for a container or closure to be considered a device, the container or closure must not merely hold the drug, but must also deliver it.[6] Thus, applying that FDA guidance to our proposed

[6] FDA guidance states the following: "The Agency draws a distinction between mere drug containers and closures and containers and closures that are also devices. The essential difference is generally whether the article is designed to deliver the drug it contains or merely to hold it. If the article merely holds the drug, it is only subject to drug CGMPs as a container or closure. An article that holds or contains a drug, but also delivers it, may also be a device subject to the device QS regulation in addition to the requirements relating to drug containers and closures." FDA, Guidance for Industry and FDA Staff: Current Good Manufacturing

approach, a patent that claims packaging or a container that does not deliver a drug would not meet the standard for listing because the item it claims would not meet the definition of a device and thus could not be considered a drug-device combination product when used with the drug.

Alternatively, if FDA does not adopt our proposed approach to clarification of device patent listing requirements, from our view, the key question in assessing whether a device or device component is integral to administration of the drug should be whether deviation from the approved and patented features or uses of the device could potentially impact the safe or effective administration of the drug. If so, the device patent should be considered one that is subject to listing under section 505(b)(1) of the FDCA. FDA should not interpret § 505(b)(1) such that to demonstrate therapeutic equivalence an ANDA applicant would be required to copy patented features of a device constituent part of a drug-device combination, while at the same time the reference drug sponsor would be barred from listing the patent(s) for those same features in the Orange Book.

FDA could also clarify that NDA sponsors should consider the effect of a device or device component on bioavailability or bioequivalence in determining whether a patent claiming the device or component should be listed. Features of the drug product that are likely to affect the rate and amount of active ingredient delivered at a drug target should be given the greatest focus. For example, the configuration of mechanical components of an MDI would have a high chance of affecting the amount, rate, and other parameters of delivery of a drug to its target. Patents claiming such components or configurations are ones that should be listed because they are likely to be directly relevant to the safety and efficacy of prospective products submitted under ANDA or 505(b)(2) applications. On the other hand, the configuration of the closure system for a tablet bottle does not affect the dose that is delivered by each tablet, which supports FDA's current interpretation that patents that claim only the drug's packaging are generally not subject to listing.

BIO Response to Select "Method-of-Use Patents" Questions

- **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*

Practice Requirements for Combination Products (January 2017), available at https://www.fda.gov/media/90425/download.

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 approach to clarification of device listing requirements described above should also be applied to device method-of-use patents. Under that approach, patents that claim the active ingredient or its formulation should be subject to the listing requirement. Likewise, patents that claim the use of the active ingredient or formulation, or the use of the combined device and active ingredient/formulation, should be subject to listing, but claiming this way should not be a necessary element. As explained in greater detail in our response to the preceding question, where a method of using a device claims only the use of the device constituent part (or the use of a component thereof), the analysis would then turn on whether the device as intended to be used with the drug meets the 21 C.F.R. § 3.2(e) definition of a combination product. If it does, and that intended use is within the scope of the patent's claim, then the patent should be considered as claiming a method-of-using the drug for FDCA § 505(b)(1) and (c)(2) patent listing purposes.

If FDA does not adopt our proposed approach to clarification, in providing guidance on when a device method-of-use patent meets the FDCA standard for listing, FDA should not take into consideration whether the patent specifically claims and/or discloses the active ingredient or formulation of the approved drug. Rather, whether a patent that claims a method of using a device constituent part (or component of a device constituent part) is subject to listing should turn on whether the use is directed to the safe and effective performance of the drug product for an approved indication or condition of use. Patented characteristics of a method-of-use device of this nature are likely to be particularly relevant to design decisions of prospective generic or follow-on applicants, as well as to decisions to carve out uses from their labeling if permitted, and listing the corresponding patents is therefore important to fulfil the notice function of the Orange Book.

BIO proposes the following as potential indicators for when a patent that claims a method of using a device constituent part or component of a device constituent part is directed to the safe and effective performance of the drug product to warrant listing in the Orange Book:

- whether the device (or component part) is referenced in the label in connection with the drug's approved indication or condition of use;
- whether the device (or component part) plays a role in ensuring that a patient receives the correct or a bioequivalent dose of the specific drug;
- whether the "device" is one that FDA considers a medical device under the FDCA, and that the agency thus required be approved under the NDA for the drug product or

approved or cleared under a separate device-specific marketing authorization (or the device falls under a 510(k)-exempt classification or is subject to FDA enforcement discretion);
- whether the device (or component part) would pose a risk to patient safety if it does not function as intended; and
- whether the device's labeling states that it is for use with the specific drug.

BIO Responses to the "REMS-Related Patents" Questions

- **Question 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?*

BIO asks that FDA clarify what it considers to be a patent that claims how a sponsor has implemented a REMS. In our experience, such patents are commonly understood to be those that claim computer or database-enabled methods or systems for mitigating a drug's risk by controlling aspects of the drug's distribution, dispensing, patient compliance monitoring, prescription filling, outcomes reporting, and the like. Whether or not such a patent should be listed should depend on whether it is deemed to claim "the drug" or "a method of using the drug," and not on special rules or prohibitions that hinge on whether a REMS is implemented or not. At any rate, BIO urges FDA to make clear that it does not consider patents claiming safe methods of patient treatment or administration (e.g., marker-assisted methods for adjusting and administering drug doses) to be patents that claim a REMS.

- **Question 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?*

Please see BIO's response to REMS-Related Patents Question 1 above.

BIO Responses to the "Patents for Digital Applications" Questions

- **Question 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 determining whether*

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

Whether a patent that claims a digital application associated with an approved drug product should be subject to listing should turn on whether the patent for the digital application meets the FDCA § 505(b)(1) standard of claiming the drug or a method of using the drug. We believe it is possible that patents directed to an aspect of a digital application associated with a drug product could be drafted in such a way to qualify as either a "patent which claims the drug" or a patent "which claims a method of using such drug."

As FDA has acknowledged, certain digital applications can be subject to regulation as medical devices. FDA has recognized that certain "software functions" (a classification that includes digital applications) meet the FDCA definition of a device and are regulated by FDA. FDA has stated that "[t]he FDA applies the same risk-based approach to device software functions as the agency uses to assure safety and effectiveness for other medical devices."[7] Accordingly, for those digital applications that are medical devices, much of the rationale that BIO provides in its response to Drug Product Patents Questions 1-2 also applies to this question. Specifically, a patent claiming an aspect of a digital application should be listed in the Orange Book if it can be considered a component of the overall drug product. One factor that should be considered in this analysis is whether the digital application as labeled to be used with the drug product meets the 21 C.F.R. § 3.2(e)(3) definition of a combination product (i.e., the app is co-labeled for use with a drug and both are required to achieve the approved intended use). If it does, then a patent that claims the digital application or an aspect of the digital application likely can be considered to claim the drug product.

This inquiry should be driven by whether FDA considers that aspect of the digital application to be directed to the safety and efficacy of the administered drug substance. Where a digital application as intended to be used with a drug meets the § 3.2(e) definition of a combination product, it should be assumed to be directed to the safety and efficacy of the administration of the drug. Where a digital application as used with a drug potentially does not meet the § 3.2(e) definition of a combination product, whether FDA considers an aspect of the digital application to be relevant to the safety and efficacy of the administered drug substance can be determined by various factors, such as the following:

[7] FDA, Device Software Functions Including Mobile Medical Applications (Nov. 2019), available at https://www.fda.gov/medical-devices/digital-health/device-software-functions-including-mobile-medical-applications.

- whether the aspect of the digital application is referenced in the drug product label;
- whether the aspect of the digital application plays a role in ensuring that a patient receives the correct or a bioequivalent dose of the drug product;
- whether the aspect of the digital application's use in relation to the drug product required FDA approval and/or is subject to FDA's discretionary enforcement powers;
- whether the aspect of the digital application's functionality poses a risk to a patient's safety if the software were to not function as intended; or
- whether the aspect of the digital application impacts the functionality or performance of traditional medical devices used in connection with the administration of a drug substance.

While the foregoing most directly relates to the determination of whether a patent claiming an aspect of a digital application meets the "patents which claim the drug" prong of the § 505(b)(1) statutory standard for patent listing, certain patents covering such digital applications may also be appropriately listed in the Orange Book if they satisfy the "which claim a method of using such drug" prong of the § 505(b)(1) standard for listing. FDA's regulation governing the listing of drug patents provide that "[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."[8] Accordingly, if a digital application as labeled for use with a drug meets the § 3.2(e) definition of a combination product or if use of the digital application or an aspect thereof is otherwise referenced in the label in connection with an indication or condition of use of the drug, then it is proper to list a patent directed to such use in the Orange Book.

- **Question 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?*

We reiterate our suggestion that FDA consider convening public workshops or meetings at which questions in this nascent area could be discussed. Digital technology can only be expected to become increasingly important in drug delivery. At the same time it must be acknowledged that this new field is affected by uncertainty both from an FDA regulatory as well as patent law standpoint. Public workshops can be helpful in informing any basic framework for patent listing that FDA may put in place at the field's inception. Any guidance or clarification that FDA provides concerning patents for digital applications associated with approved drug products that meet the FDCA standard for listing in the Orange Book should be a matter of statutory interpretation, and should be driven by sound science and paramount concern for patient welfare, not extraneous policy considerations. Nonetheless, the agency

[8] 21 C.F.R. § 314.53(b).

should keep in mind that, to the extent an ANDA or 505(b)(2) applicant certifies that a listed patent that claims a digital application associated with an approved drug is invalid or will not be infringed, listing of digital application patents could ultimately result in 30-month stays of approval as well as 180-day generic market exclusivity. However, it is unlikely that such stays or exclusivity awards would be attributable to a digital application patent alone, unless it is the only one in suit. In the event of a stay of approval, the time window can also be shortened for several reasons, such as voluntary dismissal of a patent from the infringement suit, a stipulation of non-infringement, or early resolution of the parties' claims via judgment on the pleadings or summary judgment.

As far as method of use patents are concerned, where appropriate, 505(b)(2) and ANDA applicants may have the option to seek to obtain marketing approval with a label that carves-out the use associated with the digital application. Moreover, where appropriate, with respect to both types of patents, applicants may be able to obtain FDA permission to deviate from the reference product label and/or the digital application specifications by filing suitability petitions, or by choosing the 505(b)(2) over the ANDA pathway.

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Finally, as FDA works to develop guidance on these issue, we also ask that the agency clarify how it interprets the changes made by the 21st Century Cures Act to the FDCA § 503(g) combination product provisions to subject device-led combination products to certain of the FDCA § 505(b)(2) patent and exclusivity provisions.

BIO thanks FDA for the opportunity to comment on these questions. We look forward to continuing to engage with the agency as it gives consideration to these issues and develops clarifying guidance for stakeholders.

Respectfully Submitted,

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