U.S. FOOD & DRUG ADMINISTRATION

Memorandum

To: Records File for *Approved Drug Products with Therapeutic Equivalence Evaluations* ("Orange Book")

From: Kendra Stewart R.Ph., Pharm.D., Supervisor, Orange Book Staff

Kendra S. Stewart -S3

Digitally signed by Kendra S Stewart -S3
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300222579, cn=Kendra S Stewart -S3
Date: 2020.04.27 10:29:11 -04'00'

Date: April 27, 2020

Subject: Orange Book Listings for Full Prescription-to-Over-the-Counter (OTC) Switches of New Drug Applications (NDAs) 022122, 020688, 021545

The purpose of this memorandum is to describe and explain the rationale for how FDA will be listing three drug products in the Orange Book following full prescription-to-OTC switches ("full switches") of those products through approvals of supplements to the NDAs. As described below, the manner in which these products will be listed in the Orange Book represents an administrative change in practice for listing a drug product that has undergone a full switch through approval of a supplement to an NDA and aligns with previous decisions regarding the legal and regulatory effect of such a switch.

Background

On February 14, 2020, FDA approved three full switches: Voltaren Arthritis Pain (diclofenac sodium) topical gel, 1% (NDA 022122, supplement 14), Pataday Twice Daily Relief (olopatadine hydrochloride) ophthalmic solution 0.1% (NDA 020688, supplement 32) and Pataday Once Daily Relief (olopatadine hydrochloride) ophthalmic solution 0.2% (NDA 021545, supplement 22). FDA approved these three full switches through approvals of supplements to the NDAs.

For NDA 022122 for Voltaren, there are currently six approved Abbreviated New Drug Applications (ANDAs) that reference this product and no pending ANDAs. There are no patents listed for this NDA, nor any applicants eligible for 180-day exclusivity.

For NDA 020688 for Pataday Twice Daily Relief, there are currently eleven approved ANDAs, (b) (4) (b) (4) There are no patents listed for this NDA, nor any applicants eligible for 180-day exclusivity.

For NDA 021545 for Pataday Once Daily Relief, there are currently six approved ANDAs, (b) (4) The single first applicant for this product marketed on June 8, 2017 and extinguished exclusivity. Prior to the switch, there were two patents listed for this NDA, U.S. Patent Nos. 6,995,186 and 7,420,609, both of which were identified as claiming the drug product. The '186 patent additionally identified patent use code U-765, "Method of Treating Allergic Conjunctivitis."

For full switches through approval of an NDA supplement (i.e., where the NDA retains the same application number) the Orange Book staff traditionally has removed the prescription listing and product number (e.g., "Product Number: 001") from the Orange Book and created a new entry and new product number (e.g.,

"Product Number: 002") in the OTC section, giving the new product number the approval date of the supplement for the switch. As an example, before the full switch of Allegra D 12 Hour Allergy and Congestion (NDA 20786) on January 24, 2011, the prescription section of the Orange Book featured the following entry[1]:

		ALLEGRA-D 12 HOUR				
AB	+	SANOFI AVENTIS US	60MG;120MG		N020786 001	Dec 24, 1997

Following the full switch of this product, the OTC section of the Orange Book featured the following entry[2]:

		ALLEGRA-D 12 HOUR ALLERGY AND CONGESTION					
+		SANOFI AVENTIS US	60MG;120MG		N020786 002	Jan 24, 2011	Jan NEWA

Although FDA has administratively created a new product number in the Orange Book and removed the previous product number for drug products that underwent a full switch through approval of an NDA supplement, for certain relevant purposes the Agency has treated the pre- and post-full-switch products to be the same "drug" and "listed drug" within the meaning of section 505(j) of the Federal Food, Drug, and Cosmetic Act ("FD&C Act"). For example:

- Following a full switch of an NDA through approval of an NDA supplement, FDA permits holders of approved and pending ANDAs referencing the NDA to submit supplements and amendments to obtain approval of the OTC conditions of use of the drug and associated labeling. In this case, FDA does not consider the post-full-switch NDA product to be a "different listed drug" within the meaning of section 505(j)(2)(D)(i) of the FD&C Act, provided that the NDA holder does not obtain approval of the switch to OTC status in a separate NDA.[3]

- Following a full switch of an NDA through approval of an NDA supplement, FDA has not considered the post-full-switch NDA product to be a different drug for purposes of the 180-day exclusivity period under section 505(j)(5)(B)(iv) of the FD&C Act. For example, following the full switch of Allegra D 12 Hour Allergy and Congestion, FDA tentatively approved Dr. Reddy Laboratories' ANDA 076667 on the basis of 180-day exclusivity for which the first applicant submitted its ANDA and qualifying paragraph IV certification before the full switch of the NDA product.

In addition, following a full switch of an NDA through approval of an NDA supplement, FDA generally has considered the submission date of any patents that the NDA holder submitted before the full switch (and that the NDA holder continues to list following approval of the supplement for the switch) to be the original (pre-switch) submission date.[4]

We note that FDA's final rule *Abbreviated New Drug Applications and 505(b)(2) Applications*[5] codified a requirement for NDA holders to submit required patent information for a supplement "[t]o change the drug product from prescription use to over-the-counter use" (21 CFR 314.53(d)(2)(i)(C)) based on the principle that such a change "would result in a new entry in the Orange Book" (81 FR 69580 at 69601). Section 314.53(d)(2) states:

1 Approved Drug Products with Therapeutic Equivalence Evaluations 31st Annual Ed. (2011), at 204.
2 Approved Drug Products with Therapeutic Equivalence Evaluations Cumulative Supp. (Jan. 2011), at 26.
3 See Proposed Rule, Abbreviated New Drug Applications and 505(b)(2) Applications, 80 Fed. Reg. 6802, 6854 (Feb. 6, 2015).
4 See 21 CFR 314.53(d)(2).
5 81 Fed. Reg. 69580 (Oct. 6, 2016).

> (2) *Supplements.* (i) An applicant must submit patent information required under paragraph (c) of this section for a patent that claims the drug substance, drug product, or method of use for which approval is sought in any of the following supplements:
> (A) To add or change the dosage form or route of administration;
> (B) To add or change the strength; or
> (C) To change the drug product from prescription use to over-the-counter use.

The preamble to the proposed version of this rule stated that:

> Although these types of changes may not necessarily result in a submission of different patent information, by requiring an NDA holder to submit complete patent information for a supplement that, if approved, would result in a new entry in the Orange Book, we ensure that patent information listed for the new entry clearly expresses the NDA holder's view regarding which patent(s) claim the drug or a method of using the drug as approved in the supplement. For example, different strengths of a drug product may have different patent coverage with respect to method-of-use patents that claim a dosing regimen or indication. In such a case, patent information would be required to be submitted with the filing of the NDA supplement and would be required to be submitted upon approval of the NDA supplement. This submission of patent information on Forms FDA 3542a and 3542 would, among other things, identify with specificity the new method of use claimed by the patent with reference to the proposed or approved labeling, respectively, for the drug product. . . . This proposed approach fulfills the statutory requirements for patent listing set forth in section 505(b)(1) and (c)(2) of the FD&C Act and ensures that patents listed for separate entries for drug products in the Orange Book are supported by an unambiguous submission of applicable patent information.[6]

Discussion

Following the full switch of NDAs 022122, 020688, and 021545 through approval of supplements to those NDAs, FDA intends to list these products in the Orange Book by creating a new entry in the OTC section but retain the product number from the prescription section (i.e., "Product Number: 001"). FDA will not describe the new entry as "Product Number: 002," in the OTC section, which is a change from the administrative practice described above.[7] Consistent with this approach, the approval date for the product in the OTC section, described as "Product: 001," will reflect the date of approval of the NDA as a prescription product, and not approval of the supplements to the NDAs that resulted in the full switches.

Until the NDA holder submits Form FDA 3542 or until 30 days after the date of approval of the supplement (whichever comes first), FDA will carry over (i.e., continue to list) the patent information associated with the product when it was listed in the prescription section of the Orange Book. If the NDA holder timely submits Form FDA 3542 after approval of the supplement, the patent submission date for the patent information listed for the product in the OTC section of the Orange Book will reflect the original date of submission of that patent information for the product in the prescription section of the Orange Book. If the application holder timely submits Form FDA 3542 after approval of the supplement with new patent information, including a new use code associated with a previously listed patent, the patent submission date for the new patent information will be determined in accordance with 21 CFR 314.53(d)(5). With one exception described below, if the NDA holder does not submit Form FDA 3542 by the end of the 30-day period, the carried-over patent information will be removed from the Orange Book at the end of the 30-day period. If the submission of a Form FDA 3542 occurs more than 30 days after approval of a supplement, the patent submission date will be determined in accordance

6 80 Fed. Reg. at 6823.

7 [redacted] (b) (4)

with 21 CFR 314.53(d)(5), even if the patent had been previously listed for the prescription product. To preserve a first applicant's eligibility for 180-day exclusivity, any qualifying patent(s) for 180-day exclusivity will remain listed in the Orange Book for the OTC product[8] entry until the 180-day exclusivity is expired or extinguished, regardless of whether the NDA holder timely submits Form FDA 3542 after approval of the supplement.

Although a Form FDA 3542a was submitted for Pataday Once Daily Relief, no Form FDA 3542 was received within 30 days after approval of supplement 22. Moreover, as noted above, 180-day exclusivity has been extinguished, so there are no qualifying patents. Accordingly, no patent information will be listed for NDA 021545's OTC product entry, unless or until the NDA holder submits a Form FDA 3542. If a new Form FDA 3542 is submitted for Pataday Once Daily Relief in the future, the patent submission date will be determined in accordance with 21 CFR 314.53(d)(5) because it will be received more than 30 days after approval of the supplement.

The rationale for this change in administrative practice is to better align the description of these products in the Orange Book with the Agency's view that a full switch through approval of a supplement to an NDA does not create a new "listed drug" under section 505(j)(2)(D)(i), does not create a new period of 180-day exclusivity (or eliminate an existing period of exclusivity), and generally does not alter the submission date of any patents that were previously submitted for the NDA and then timely resubmitted after the full switch. Although FDA's administrative practices with respect to how drugs are listed in the Orange Book are not necessarily determinative of how the Agency will implement certain provisions in section 505 of the FD&C Act and its regulations, FDA is aware that certain drug sponsors have argued that these practices have legal significance.[9]

We also note that this change in administrative practice is consistent with the requirements of 21 CFR 314.53(d)(2) and related language in the preamble to the proposed rule. Both the prior Orange Book practice (i.e., creation of an entry in the OTC section for "Product: 002") and the new practice (i.e., creation of an entry in the OTC section for "Product: 001") are consistent with the proposed rule preamble's statement that changes including a full switch "would result in a new entry in the Orange Book"; both practices result in the creation of a "new entry" in the OTC section, and the preamble did not specifically address the more granular practice of creating a "Product: 002" versus creating a new entry for "Product: 001." When an NDA holder obtains approval of a full switch through approval of an NDA supplement, it is reasonable to expect that the patent information previously submitted would be likely to require updating. For example, a method-of-use patent covering an existing prescription use might need to be removed, and the NDA holder might seek to submit new patents to cover the changed conditions of use. Section 314.53(d)(2)(i)(C)'s patent submission requirement ensures that the new entry in the OTC section contains complete and accurate patent information for the drug following the full switch.

8 The qualifying patent(s) will be signaled for delisting, consistent with Orange Book's current practice when an NDA holder requests to remove a patent or patent information and one or more first applicants are eligible for 180-day exclusivity based on a paragraph IV certification to that patent. This process will be undertaken even in the absence of a formal patent delisting request from the NDA holder.

9 See, e.g., Letter to Kathleen Uhl, MD, Acting Director, Office of Generic Drugs, FDA, from Kurt R. Karst (June 3, 2014) (arguing that the late listing of patents following the switch of Allegra D 12-Hour Allergy and Congestion had certain implications for 180-day exclusivity and pediatric exclusivity related to patents originally submitted before the full switch).