EXHIBIT A

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

Docket No. FDA-2014-N-0087

SENT VIA EMAIL

Dear Dexmedetomidine Hydrochloride Injection NDA Holder/ANDA Applicant:

On January 15, 2014, the U.S. Food and Drug Administration (FDA or the agency) established a public docket to solicit comment on certain legal and regulatory issues that pertain to Precedex (dexmedetomidine hydrochloride injection, 100 mcg (base)/mL packaged in 200 mcg (base)/2 mL single-dose vials). As described in detail below, FDA also sent a letter describing the issue to Hospira, Inc. (Hospira), the holder of New Drug Application (NDA) No. 21-038 for Precedex and to all applicants that submitted Abbreviated New Drug Applications (ANDAs) to FDA referencing Precedex. The letter also was posted on the website for FDA's public dockets at http://www.regulations.gov.

Today's letter reflects FDA's determinations with respect to permissibility of labeling carve outs for ANDAs referencing Precedex. For the reasons set forth below, FDA concludes that regardless of whether the original use code or the revised use code applies, the agency can approve an ANDA that submits a "section viii" statement and omits labeling that discloses the protected use (as identified by Hospira). FDA further concludes that such omissions do not render the drug less safe or effective for the remaining non-protected conditions of use.

I. FACTUAL BACKGROUND

In the letters sent to NDA holder Hospira and ANDA applicants and posted to the docket, FDA noted the following:

Precedex is approved for the following indications:

1. Sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting. Administer Precedex by continuous infusion not to exceed 24 hours.

2. Sedation of non-intubated patients prior to and/or during surgical and other procedures.

Hospira has, over time, listed several patents covering the Precedex product referenced above. Only a method-of-use patent remains: U.S. Patent No. 6,716,867 (the '867 patent), which expires (including a pediatric exclusivity period) on October 1, 2019.[1]

[1] U.S. Patent No. 4,910,214 expired on July 15, 2013, and an associated pediatric exclusivity period expired on January 15, 2014.

Hospira originally listed the '867 patent in May 2004 with the following use code (U-572): "Intensive care unit sedation." In November 2008, Hospira listed U.S. Patent No. 5,344,840 (the '840 patent) with the following use code (U-912) in the Orange Book: "Sedation of non-intubated patients prior to and/or during surgical and other procedures." That patent expired on September 6, 2011. On January 6, 2014, Hospira sought to amend the '867 patent use code to "intensive care unit sedation, including sedation of non-intubated patients prior to and/or during surgical and other procedures." FDA, in accordance with the ministerial manner in which it implements patent use code information, changed the use code on January 8, 2014.

FDA sought comments on the following issues:

1. Does the breadth of the new use code description for the '867 patent foreclose ANDA applicants from gaining approval for any of the approved indications (or for any subset of those indications) before the '867 patent expires? For example, would it be permissible as a scientific, regulatory, and legal matter for an ANDA applicant to submit a statement under 21 U.S.C. §355(j)(2)(A)(viii) and a corresponding carve out that results in an approval for a subset of the second approved indication, *i.e.*, an approval explicitly limited to procedures outside of an intensive care setting? In this context, is it acceptable to add new words to the approved indication to limit the indication to exclude only that portion of the indication that is covered by the use code (i.e., to exclude sedation of non-intubated patients in the ICU setting only)? If you believe a carve out of this type is permissible, if you wish, you may submit a side by side of the indication section of the labeling for dexmedetomidine hydrochloride injection showing the carve out that you believe would be acceptable.

2. Whether the fact that Hospira changed the use code information outside of the 30-day window after the patent issued means that the use code change is late listed as to any ANDAs pending with a section viii statement at the time the use code was changed. *See* 21 C.F.R. § 314.53(c), (d). If so, would any ANDA with an existing section viii statement be entitled to retain that statement (and corresponding carve out) under 21 C.F.R. § 314.94(a)(12)(vi), notwithstanding the change in use code?

3. What relevance, if any, to a determination of whether the use code change was timely submitted is the fact that Hospira previously listed the '840 patent with very similar use code information to that now listed for the '867 patent, and did not change the use code for the '867 patent until after the '840 patent expired?[2]

FDA requested a response by close of business on January 24, 2014. Commenters submitting in the initial comment period had an opportunity to respond to comments from other commenters by close of business January 31, 2014. The agency received 22 comments, which can be accessed at http://www.regulations.gov.

[2] Dear Applicant Letter from FDA Center for Drug Evaluation and Research to Hospira Inc. re. Dexmedetomidine Hydrochloride Injection NDA ANDA , Docket No. FDA-2014-N-0087 (Jan. 15, 2014).

II. LEGAL AND REGULATORY BACKGROUND

A. The Statutory and Regulatory Framework for Patent Protection for NDAs and for Labeling Differences for ANDAs

The Federal Food, Drug, and Cosmetic Act (the FD&C Act) and FDA regulations require that a sponsor seeking to market an innovator drug submit an NDA. NDAs contain, among other things, extensive scientific data demonstrating the safety and effectiveness of the drug for the indication for which approval is sought.[3] Under the statute, an NDA applicant also must submit to FDA a list of patents claiming the approved drug substance or drug product, or claiming an approved method of using the drug product in the NDA. Specifically, section 505(b)(1) of the FD&C Act requires an NDA applicant to file as part of the NDA "the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or *which claims a method of using such drug* and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug."[4] FDA is required to publish this patent information[5] and does so in the publication titled *Approved Drug Products with Therapeutic Equivalence Evaluations*, commonly known as the Orange Book.

The statute also provides that if a relevant patent is issued after NDA approval, the NDA sponsor must file the required patent information with FDA not later than 30 days after the date the patent is issued.[6] FDA's regulations further require that an applicant seeking approval of certain supplements, including a supplement for a new indication, submit with its supplement the patent information required for NDA approvals for a patent that claims the drug, drug product, or method of use.[7]

A drug product with an effective approval under section 505(c) or 505(j) of the FD&C Act is known as a "listed drug."[8] Under the *Drug Price Competition and Patent Term Restoration Act of 1984* (Public Law 98-417) (the Hatch-Waxman Amendments), an applicant may submit an ANDA under section 505(j) of the FD&C Act for approval of a generic version of a listed drug previously approved under section 505(c).[9] The ANDA approval process shortens the time and

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[3] Section 505(b)(1) of the FD&C Act.

[4] Sections 505(b)(1) of the FD&C Act (emphasis added). See also 21 CFR 314.53(c)(2)(ii).

[5] Section 505(b)(1), (c)(2) and (j)(7) of the FD&C Act.

[6] Section 505(c)(2) of the FD&C Act; 21 CFR 314.53.

[7] 21 CFR 314.53(d)(2).

[8] Under 21 CFR 314.3(b), "[l]isted drug means a new drug product that has an effective approval under section 505(c) of the act for safety and effectiveness or under section 505(j) of the act, which has not been withdrawn or suspended under section 505(e)(1) through (e)(5) or (j)(5) of the act, and which has not been withdrawn from sale for what FDA has determined are reasons of safety or effectiveness." A listed drug is identified as having an effective approval in the Orange Book, which includes patent information for each drug approved under 505(c). 21 CFR 314.53(e).

[9] *Drug Price Competition and Patent Term Restoration Act of 1984,* Pub. L. No. 98-417, 98 Stat. 1585.

effort needed for approval by, among other things, allowing an ANDA applicant to rely on FDA's previous finding of safety and effectiveness for a listed drug rather than requiring the ANDA applicant to independently demonstrate the safety and effectiveness of its proposed drug. To rely on such a finding, the ANDA applicant must show that its proposed drug product is the same as the listed drug in many respects (including active ingredient, dosage form, strength, route of administration, and, with certain exceptions, labeling), and that its product is bioequivalent to the listed drug.

The ANDA applicant must identify the listed drug on which it seeks to rely for approval. As described in more detail below, the timing of ANDA approval depends on, among other things, any patent protection for the listed drug that the ANDA references and whether the ANDA applicant challenges those patents.[10] In general, an ANDA may not obtain final approval until listed patents and marketing exclusivity have expired or until NDA holders and patent owners have had the opportunity to defend relevant patent rights in court.

Specifically, with respect to each patent submitted by the sponsor for the listed drug and listed in the Orange Book, the ANDA applicant generally must submit to FDA one of four specified certifications under section 505(j)(2)(A)(vii) of the Act. The certification must state one of the following:

(I) that such patent information has not been filed (a paragraph I certification),
(II) that such patent has expired (a paragraph II certification),
(III) the date on which such patent will expire (a paragraph III certification), or
(IV) that such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted (a paragraph IV certification).[11]

The purpose of this requirement is "to give notice, if necessary, to the patent holder so that any legal disputes regarding the scope of the patent and the possibility of infringement can be resolved as quickly as possible."[12]

If an applicant files a paragraph I or II certification, the patent in question (there is none in the case of a paragraph I certification) will not be a barrier to ANDA approval. If an applicant files a paragraph III certification, the applicant agrees to wait until the relevant patent has expired before seeking final approval of its ANDA. If, however, an applicant wishes to seek approval of its ANDA before a listed patent has expired by challenging the validity of a patent or claiming that a patent would not be infringed by the product proposed in the ANDA or is unenforceable, the applicant must submit a paragraph IV certification to FDA. An applicant submitting a paragraph IV certification to a listed patent must provide the NDA holder and each patent owner with notice of its patent certification, including a description of the legal and factual basis for the ANDA holder's assertion that the patent is invalid or not infringed.[13]

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[10] See section 505(b), (c), (j)(2)(A)(vii), and (j)(5)(B) of the FD&C Act.

[11] Section 505(j)(2)(A)(vii) of the FD&C Act; see also 21 CFR 314.94(a)(12)(i)(A).

[12] *Torpharm, Inc. v. Thompson*, 260 F. Supp. 2d 69, 71 (D.D.C. 2003).

[13] Section 505(j)(2)(B) of the FD&C Act.

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