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**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**Food and Drug Administration**

[Docket No. FDA-2008-N-0482]

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Certifier J. Corbin

**Ophthalmic Balanced Salt Solutions for Ocular Surgical Procedures;  
Enforcement Action Dates**

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Notice.

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**SUMMARY:** The Food and Drug Administration (FDA) is announcing its intention to take enforcement action against unapproved ophthalmic balanced salt solutions for irrigation of the eye during surgery and persons<sup>1</sup> who manufacture or cause the manufacture of such products or their shipment in interstate commerce. Unapproved ophthalmic balanced salt solutions have been associated with adverse events, some of them leading to permanent loss of visual acuity, because of contamination of the product or other product defects. Ophthalmic balanced salt solutions are new drugs that require approved applications because they are not generally recognized as safe and effective. Two firms have approved applications to market these products. Manufacturers who wish to market ophthalmic balanced salt solutions must obtain FDA approval of a new drug application (NDA) or an abbreviated new drug application (ANDA).

**DATES:** This notice is effective [*insert date of publication in the Federal Register*]. For information about enforcement dates, see **SUPPLEMENTARY INFORMATION**, section III.B.

<sup>1</sup> A "person" includes individuals, partnerships, corporations, or associations (21 U.S.C. 321(e)).

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**ADDRESSES:** All communications in response to this notice should be identified with Docket No. FDA-2008-N-0482 and directed to the appropriate office listed as follows:

*Regarding applications under section 505(b) of Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355(b)):* Division of Anti-Infective and Ophthalmology Products, Office of New Drugs, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, Silver Spring, MD 20993-0002.

*Regarding applications under section 505(j) of the act:* Office of Generic Drugs, Center for Drug Evaluation and Research (HFD-600), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855.

*All other communications:* Jennifer Devine, Center for Drug Evaluation and Research (HFD-310), Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 5240, Silver Spring, MD 20993-0002.

**FOR FURTHER INFORMATION CONTACT:** Jennifer Devine, Office of Compliance, Division of New Drugs and Labeling Compliance, Center for Drug Evaluation and Research (HFD-310), Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 5240, Silver Spring, MD 20993-0002, 301-796-3347, e-mail: [Jennifer.Devine@fda.hhs.gov](mailto:Jennifer.Devine@fda.hhs.gov).

**SUPPLEMENTARY INFORMATION:**

**I. Background**

Ophthalmic balanced salt solutions are sterile, isotonic irrigating solutions used during surgical procedures on the eye. Prior to the 1960s, saline was the ophthalmic irrigating solution most commonly used to replace small amounts of intraocular fluid and wet the external eye. Balanced salt solutions for use during ocular surgery were developed in the 1960s to provide a temporary

replacement for the aqueous humor, physiologically supporting the cornea until sufficient fluid is replaced by the ciliary body. These products enable the conduct of complex intraocular surgery techniques that require the replacement of large amounts of aqueous and vitreous humor. Some of the products marketed today are designed for use in surgical procedures of limited duration, while others are appropriate for use in procedures of any expected duration.

Two firms—Alcon Laboratories and Akorn, Inc. (Adorn),—have approved applications for ophthalmic balanced salt solutions. Alcon’s approved products are marketed under the names BSS (NDA 20–742), intended for surgeries of under 60 minutes, and BSS-plus (NDA 18–469), intended for surgery of any expected duration. Akorn’s approved products include Balanced Salt Solution (ANDA 75–503) and Endosol Extra (NDA 20–079). BSS, BSS-plus, and Endosol Extra have been designated as reference listed drugs, meaning that FDA can accept ANDAs referencing these products and filed under section 505(j) of the Federal, Food, Drug, and Cosmetic Act (act). In addition, the agency is aware that other firms market unapproved ophthalmic balanced salt solutions.

## **II. Safety Issues Associated With Ophthalmic Balanced Salt Solutions.**

Serious safety concerns associated with ophthalmic balanced salt solutions are mentioned in adverse drug events reported to the agency and in the literature. Through January 31, 2008,<sup>2</sup> FDA had received over 300 spontaneous reports of serious adverse events associated with all ophthalmic balanced salt solution products. Adverse events associated with these products that have been reported to FDA include toxic anterior segment syndrome (TASS) (a noninfectious inflammation of the anterior segment of the eye), bacterial

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<sup>2</sup> Data in the current system date back to 1969, when FDA first implemented an adverse event reporting system.

endophthalmitis, corneal edema, and corneal opacity (clouding). In some cases, these adverse events have resulted in permanent loss of visual acuity. Because the adverse event reports sometimes include limited information on the product used, it is often difficult to establish whether an adverse event was caused by a particular product. In some instances, adverse events may be the result of improperly manufactured products. Product defects affecting the safety and performance of ophthalmic balanced salt solutions include contaminants (such as bacteria, endotoxins, fungi, or particulates) and variations in pH and osmolality.<sup>3</sup> In 2006, for example, contamination with endotoxins of unapproved products made by one manufacturer was associated with several hundred reports of adverse events (both serious and nonserious), including TASS. Given the safety concerns described previously, FDA's review of the individual applications and application supplements for ophthalmic balanced salt solutions, including their manufacturing methods and controls, is essential to ensuring the safety, efficacy, and quality of these products.

### **III. Legal Status**

#### *A. Ophthalmic Balanced Salt Solutions Are New Drugs Requiring Approved Applications*

As described previously, ophthalmic balanced salt solution products used for irrigation of the eye during surgery are not generally recognized as safe and effective under section 201(p) of the act (21 U.S.C. 321(p)). Therefore, ophthalmic balanced salt solution products are regarded as new drugs as defined in section 201(p) of the act and are subject to the requirements of section 505 of the act. As set forth in this notice, approval of an NDA or an

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<sup>3</sup> McDermott, M.L., H.F. Edelhauser, H.M. Hack, and R.H.S. Langston, "Ophthalmic Irrigants: A Current Review and Update," *Ophthalmic Surgery*, 19(10):724-733, 1988; Briggs, R.B. and D.L. McCartney, "Balanced Salt Solution Infusion Alert," *Archives of Ophthalmology*, 106:718, 1988.

ANDA under section 505 of the act is required as a condition for manufacturing or marketing all ophthalmic balanced salt solutions. After the dates identified in this notice, FDA intends to take enforcement action against unapproved ophthalmic balanced salt solutions and persons who cause the manufacture or interstate shipment of such products. Any person who submits an application for an ophthalmic balanced salt solution but has not received approval must comply with this notice.

*B. Notice of Enforcement Action*

Although not required to do so by the Administrative Procedure Act, the act, or any rules issued under its authority, or for any other legal reason, FDA is providing this notice to persons who are marketing unapproved ophthalmic balanced salt solution products that the agency intends to take enforcement action against such products and those who manufacture them or cause them to be manufactured or shipped in interstate commerce.

Manufacturing or shipping unapproved ophthalmic balanced salt solution products can result in enforcement action, including seizure, injunction, or other judicial or administrative proceeding. Consistent with policies described in the agency's guidance entitled "Marketed Unapproved Drugs—Compliance Policy Guide" (the Marketed Unapproved Drugs CPG), the agency does not expect to issue a warning letter or any other further warning to firms marketing unapproved ophthalmic balanced salt solution products prior to taking enforcement action. The agency also reminds firms that, as stated in the Marketed Unapproved Drugs CPG, any unapproved drug marketed without a required approved drug application is subject to agency enforcement action at any time. The issuance of this notice does not in any way obligate the agency

to issue similar notices or any notice in the future regarding marketed unapproved drugs.<sup>4</sup>

As described in the Marketed Unapproved Drugs CPG, the agency may, at its discretion, identify a period of time during which the agency does not intend to initiate an enforcement action against a currently marketed unapproved drug solely on the ground that it lacks an approved application under section 505 of the act. With respect to unapproved ophthalmic balanced salt solution products, the agency intends to exercise its enforcement discretion for only a limited period of time because ophthalmic balanced salt solution products are drugs with potential safety risks and approved ophthalmic balanced salt solutions for use in surgical procedures of both shorter and longer durations have been available since 1997. Therefore, the agency intends to implement this notice as follows.

For the effective date of this notice, see the **DATES** section of this document. FDA intends to take enforcement action to enforce section 505(a) of the act against any unapproved ophthalmic balanced salt solution product that is not listed with the agency in full compliance with section 510 of the act (21 U.S.C. 360) before [*insert date of filing at the **Federal Register***], and is manufactured, shipped, or otherwise introduced or delivered for introduction into interstate commerce by any person on or after [*insert date of publication in the **Federal Register***]. FDA also intends to take enforcement action to enforce section 505(a) of the act against any unapproved ophthalmic balanced salt solution that is listed with FDA in full compliance with section 510 of the act but is not being

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<sup>4</sup> The agency's general approach for dealing with these products in an orderly manner is spelled out in the Marketed Unapproved Drugs CPG. That CPG, however, provides notice that any product that is being marketed illegally, and the persons responsible for causing the illegal marketing of the product, are subject to FDA enforcement action at any time.

commercially used or sold<sup>5</sup> in the United States on [*insert date of filing at the Federal Register*] and that is manufactured, shipped, or otherwise introduced or delivered for introduction into interstate commerce by any person on or after [*insert date of publication in the Federal Register*].

However, for unapproved ophthalmic balanced salt solution products that are commercially used or sold in the United States, have a National Drug Code (NDC) number listed with FDA, and are in full compliance with section 510 of the act before [*insert date of filing at the Federal Register*] (“currently marketed and listed”), the agency intends to exercise its enforcement discretion as follows. FDA intends to initiate enforcement action against any currently marketed and listed unapproved ophthalmic balanced salt solution product that is manufactured on or after [*insert date 60 days after date of publication in the Federal Register*] or that is shipped on or after [*insert 120 days after date of publication in the Federal Register*].<sup>6</sup> Further, FDA intends to take enforcement action against any person who manufactures or ships such products after these dates. Any person who has submitted or submits an application for an ophthalmic balanced salt solution product but has not received approval must comply with this notice.

The agency, however, does not intend to exercise its enforcement discretion as outlined previously if the following apply: (1) A manufacturer

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<sup>5</sup> For the purposes of this notice, the term “commercially used or sold” means that the product has been used in a business or activity involving retail or wholesale marketing and/or sale.

<sup>6</sup> If FDA finds it necessary to take enforcement action against a product covered by this notice, the agency may take action relating to all of the defendant’s other violations of the act at the same time. For example, if a firm continues to manufacture or market a product covered by this notice after the applicable enforcement date has passed, to preserve limited agency resources, FDA may take enforcement action relating to all of the firm’s unapproved drugs that require applications at the same time (see, e.g., *United States v. Sage Pharmaceuticals*, 210 F.3d 475, 479–480 (5th Cir. 2000) (permitting the agency to combine all violations of the act in one proceeding, rather than taking action against multiple violations of the act in “piecemeal fashion”)).

or distributor of an unapproved ophthalmic balanced salt solution product covered by this notice is violating other provisions of the act, including but not limited to, violations related to FDA's current good manufacturing practices, adverse drug event reporting, labeling or misbranding requirements or (2) it appears that a firm, in response to this notice, increases its manufacture or interstate shipment of ophthalmic balanced salt solution products above its usual volume during these periods.

Nothing in this notice, including FDA's intent to exercise its enforcement discretion, alters any person's liability or obligations in any other enforcement action, or precludes the agency from initiating or proceeding with enforcement action in connection with any other alleged violation of the act, whether or not related to an unapproved drug product covered by this notice. Similarly, a person who is or becomes enjoined from marketing unapproved drugs may not resume marketing of unapproved ophthalmic balanced salt solution products based on FDA's exercise of enforcement discretion that is set forth in this notice.

Drug manufacturers and distributors should be aware that the agency is exercising its enforcement discretion as described previously only in regard to ophthalmic balanced salt solution products that are marketed under an NDC number listed with the agency in full compliance with section 510 of the act before [*insert date of filing at the Federal Register*]. As previously stated, unapproved ophthalmic balanced salt solution products that are currently marketed but not listed with the agency on the date of this notice must, as of the effective date of this notice, have approved applications prior to their shipment in interstate commerce. Moreover, any person or firm that has

submitted or submits an application but has yet to receive approval for such products is still responsible for full compliance with this notice.

### *C. Discontinued Products*

Some firms may have previously discontinued the manufacturing or distribution of products covered by this notice without removing them from the listing of their products under section 510(j) of the act. Other firms may discontinue manufacturing or marketing listed products in response to this notice. Firms that wish to notify the agency of product discontinuation should send a letter, signed by the firm's chief executive officer, fully identifying the discontinued product(s), including NDC number(s), and stating that the product(s) has (have) been discontinued. The letter should be sent to Jennifer Devine (see **ADDRESSES**). Firms should also update the listing of their products under section 510(j) of the act to reflect discontinuation of unapproved ophthalmic balanced salt solution products. FDA plans to rely on its existing records, including drug listing records, or other available information when it targets violations for enforcement action.

This notice is issued under the Federal Food, Drug, and Cosmetic Act (sections 502 and 505 (21 U.S.C. 352)) and under authority delegated to the Deputy Commissioner for Policy under section 1410.10 of the FDA Staff Manual Guide.

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Dated: 9/8/08

September 8, 2008.

  
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Jeffrey Skuren,  
Associate Commissioner for Policy and Planning.

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