November 30, 2011

Margaret A. Hamburg, M.D.
Commissioner of Food and Drugs
10903 New Hampshire Avenue
Silver Spring, Maryland 20993

Re: Docket FDA-2011-N-0513

Dear Dr. Hamburg:

The Center for Drug Evaluation and Research (CDER) is writing in response to your November 7, 2011 letter in the above-captioned proceeding. CDER asks that you defer action on the hearing request from ISTA Pharmaceuticals, Inc. (ISTA) regarding CDER’s proposed refusal to approve a supplemental new drug application for a larger fill size of Bromday (bromfenac ophthalmic solution) 0.09% until after the Dermatologic and Ophthalmic Drugs Advisory Committee (DODAC) meeting on February 27, 2012.¹ On that date, the DODAC will advise CDER on the general issue of whether the use of a single bottle of certain ophthalmic drug products to treat two eyes presents an increased risk of microbial cross-contamination and, if so, whether that risk can be mitigated through changes in labeling, container configuration, or other means. DODAC’s input is important to resolving this proceeding in the most scientifically sound manner. Therefore, deferral is in the best interest of public health. It is also most consistent with the efficient use of limited agency resources.

Should you decide you must act on ISTA’s hearing request in advance of the DODAC meeting, CDER respectfully requests an opportunity to provide a detailed written explanation of

¹ Dermatologic and Ophthalmic Drugs Advisory Committee; Notice of Meeting, 76 Fed. Reg. 71349 (Nov. 17, 2011).
its proposal not to approve the ISTA supplement and a thorough analysis of ISTA’s factual and legal allegations before you act.

I. **Background**

FDA approved ISTA’s new drug application (NDA) 21–664 to market Xibrom (bromfenac sodium ophthalmic solution) 0.09% on March 24, 2005. On October 16, 2010, FDA approved a second product, Bromday (bromfenac ophthalmic solution) 0.09%, through a supplement to NDA 21–664. Xibrom and Bromday have the same active ingredient, are both topical ophthalmic solutions supplied as sterile, aqueous eye drops, and are both approved for the treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract extraction. The products have different dosing regimens: Xibrom is applied to the affected eye twice daily for 2 weeks beginning 24 hours after surgery, whereas Bromday is applied to the affected eye once daily beginning 1 day before surgery and continuing on the day of surgery and for 14 days thereafter.

Bromday is currently approved in a 1.7 mL fill size. ISTA submitted Supplement 15 to the Xibrom/Bromday NDA on October 18, 2010, seeking approval to market Bromday in a 2.4 mL fill size. ISTA has stated that patients often have cataract removal surgeries in both eyes, and that the 2.4 mL fill size should be approved for these patients, because the 1.7 mL fill size does not contain a sufficient volume of product to provide a full course of treatment for two eyes. The Division of Anti-Infective and Ophthalmology Products (now the Division of Transplant and Ophthalmology Products) issued a complete response letter regarding Supplement 15 on

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2 ISTA contends that Xibrom and Bromday are a single drug product in its lawsuit against FDA seeking to block generic competition. *ISTA v. FDA*, No. 11-0907 (JSG) (D.D.C.) (filed July 1, 2011). ISTA further contends in that suit that CDER’s recent approval of a generic version of Xibrom was improper because it was inconsistent with CDER’s concerns about the larger container size of Bromday. While a larger size of the generic product was approved, it is not currently marketed.
February 18, 2011. The letter stated that the current fill volume of 1.7 mL appears to contain sufficient drug product for a full course of treatment (in a single eye), and that a single bottle of Bromday should not be used to treat more than one eye in a postoperative setting.

ISTA had at least four options for responding to the complete response letter: (1) resubmit the supplement, addressing the deficiencies identified by the agency; (2) withdraw the supplement; (3) seek formal dispute resolution through one or more appeals above the division level; or (4) request an opportunity for a hearing. On May 12, 2011, ISTA went directly to the fourth of these options, requesting an opportunity for a hearing on whether there are grounds under section 505(d) of the Federal Food, Drug, and Cosmetic Act (the Act) for the agency to deny approval of Supplement 15.

In response to ISTA’s request, CDER gave ISTA written notice of an opportunity for a hearing (NOOH), which was published in the Federal Register on August 3, 2011. The NOOH noted CDER’s view that use of a single bottle of Bromday to treat two eyes may pose an increased risk of microbial infection. It also indicated that CDER proposed postponing its decision on ISTA’s request for an NOOH until after an advisory committee could meet on the issue, but ISTA did not accept this proposal. The NOOH further stated CDER’s determination that ISTA has not provided sufficient data, analysis, and information to support a determination that Bromday would be safe if supplied in the proposed larger fill size, as required under the Act and FDA regulations.

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3 21 CFR 314.110(b); Guidance for Industry, Formal Dispute Resolution: Appeals Above the Division Level (Feb. 2000).


5 21 USC 355(b)(1)(A) and (d)(4); 21 CFR 314.125(b)(4).
ISTA submitted a request for hearing on August 3, 2011, and a “brief” in support of its request on September 30, 2011. The next step in this administrative process is for CDER to prepare and submit to the Commissioner an analysis of ISTA’s hearing request, a recommendation regarding whether or not to grant the request, and a “proposed order ruling on the matter” for the Commissioner’s consideration. If granted, the hearing would be a formal evidentiary public hearing under Part 12.

II. Request for Deferral

In the interest of public health, CDER asks the Commissioner to defer action on the ISTA hearing request until after CDER obtains the advice of the DODAC on February 27, 2012. CDER has determined that the advice of outside experts in ophthalmology would be highly beneficial to its regulatory decision-making on post-operative topical ophthalmic products, including the issues raised by ISTA in connection with Supplement 15. The DODAC includes six ophthalmologists, including two with special expertise in corneal and external disease. The DODAC is the most appropriate forum in which to fully consider cross-contamination risk and mechanisms for addressing it, particularly given the clinical practice experience of the DODAC.

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6 21 CFR 314.200(f). There is no express deadline for submission of CDER’s analysis and proposed order, although the statute and regulations provide that, if the Commissioner decides to grant a hearing, the hearing should begin within 90 days of the due date for ISTA’s hearing request unless the parties agree otherwise. 21 USC 355(c)(1)(B); 21 CFR 314.200(g)(5). Here, the deadline for ISTA’s hearing request was September 3, 2011, which means that, if the Commissioner were to grant the request, the hearing could begin as early as approximately December 1, 2011. Although CDER asked ISTA to agree to an extension of this deadline in order to facilitate CDER consultation with the DODAC, ISTA declined to do so. In a letter to your office dated November 18, 2011, the company stated that “[w]ithout waiving its right to a hearing in the timeline specified by statute, ISTA would be willing to discuss with the Office of the Commissioner and counsel for CDER an appropriate timeline for conducting and concluding these proceedings.”

7 21 USC 355(d); 21 CFR 12.21(a), 12.24(b)(1) and (c), and 314.200(g).

members. The information presented at the DODAC meeting and the DODAC’s advice may facilitate resolution of this matter without the need for a hearing.

Postponement of action on ISTA’s hearing request is also appropriate because CDER has become aware that ISTA recently began marketing a “twin pack” configuration of Bromday, which consists of two 1.7 mL bottles packaged together in a single carton. 9 Such a configuration, in which a separate bottle would be used for each eye, would seem to be a potentially acceptable way to mitigate cross-contamination risk, provided it were appropriately labeled and met all other legal and regulatory requirements.

Under these circumstances, it would be an inefficient use of limited agency resources to proceed to a formal evidentiary hearing at this time. CDER has endeavored in good faith to resolve this issue by encouraging ISTA to seek dispute resolution -- the mechanism best suited to resolving scientific and procedural disputes with sponsors fairly and expeditiously -- which the company declined. We also asked ISTA to agree to postpone the deadline for CDER’s response to the company’s request for an opportunity for hearing, and later, to postpone this proceeding to allow CDER to obtain the advice of the DODAC, but the company has not agreed to either postponement. 10 CDER is concerned that proceeding directly to a hearing in this case could encourage other sponsors to take the same approach which, given the resource-intensive nature of a formal evidentiary hearing, would divert Agency resources from other important public health priorities and therefore would not be compatible with FDA’s public health mission.

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III. ISTA’s Hearing Request

Threshold for Oral Evidentiary Hearing: If you decline to defer action on ISTA’s hearing request, we note that ISTA is not automatically entitled to a hearing; the company must raise a “genuine and substantial issue of fact.” This threshold showing is required by FDA regulations, which provide that the person requesting a hearing “is required to set forth specific facts showing that there is a genuine and substantial issue of fact that requires a hearing.” In the absence of such a showing, the Commissioner “will enter summary judgment against” the person.

This standard parallels the standard for summary judgment in federal court. The party requesting a hearing “may not rely upon allegations or denials” to create an issue of fact. Rather, it must present evidence that establishes the existence of a disputed fact that might affect the outcome of the proceeding. Otherwise, the purpose of summary judgment would be “severely undercut.”

ISTA has not presented any such evidence. The only information the company has supplied is its analysis of data in the Adverse Event Reporting System (AERS). Specifically, ISTA contends that an absence of such reports is tantamount to an affirmative finding that a
product is safe.\textsuperscript{16} CDER disagrees that an absence of spontaneous adverse reports equates to an affirmative finding of safety. Further, in many cases, AERS reflects significant under-reporting of adverse drug experiences. CDER expects that bacterial infection following ophthalmic surgery may be even less likely to be reported in AERS than other adverse experiences, because CDER is not aware of significant usage of a single bottle of ophthalmic drug product to treat more than one eye in a post-operative setting, and because many practitioners and patients may not link an ophthalmic infection to a post-surgical drug, even if such a link is warranted.

ISTA cites the Supreme Court's decision in \textit{Weinberger v. Hynson, Westcott and Dunning}\textsuperscript{17} in support of its contention that "the law requires that FDA grant ISTA a hearing."\textsuperscript{18} ISTA misconstrues both the law and the Court's decision in that case. In \textit{Hynson}, the Court confirmed that FDA may decline to grant a hearing when a sponsor fails to raise a genuine and substantial issue of fact, because holding a hearing under those circumstances would be "an exercise in futility" and impair the agency's ability to protect the public health.\textsuperscript{19} ISTA also cites \textit{American Cyanamid v. FDA}\textsuperscript{20}, which characterizes \textit{Hynson} as holding that denial of a hearing is improper only "where the regulations are so imprecise that it is not possible to say confidently from the face of the submission that the standards have not been met." The company argues that Section 505(d)(1) of the Act, which requires an application to include "adequate tests by all

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\item[\textsuperscript{16}] Submission of ISTA Pharmaceuticals, Inc. in Response to NOOH ("ISTA Submission") (Sept. 30, 2011) at 13 (arguing that "adverse event data for Xibrom and similar drugs demonstrate no risk from using a single bottle for two eyes").
\item[\textsuperscript{17}] 412 U.S. 618, 621 (1973).
\item[\textsuperscript{18}] ISTA Submission at 26.
\item[\textsuperscript{19}] 412 U.S. at 621.
\item[\textsuperscript{20}] 606 F.2d 1307, 1312 (D.C. Cir. 1979).
\end{itemize}
methods reasonably applicable to show whether or not [a] drug is safe,” is the operative standard and is sufficiently vague that the Commissioner cannot deny a hearing.

CDER does not agree with ISTA’s argument. First, paragraph (1) of Section 505(d) is not the dispositive standard here. For example, paragraph (4) of that section authorizes the agency to deny approval of an application if it “has insufficient information to determine whether [a] drug is safe[.]” Moreover, under either authority, ISTA has -- as noted above and in the NOOH -- failed to supply any data or information to address CDER’s concern about cross-contamination risk. It is therefore apparent from the face of the company’s submission that Supplement 15 does not meet the threshold for approval, and that the Commissioner may deny a hearing in this matter.

Consistency of Treatment. ISTA also argues that CDER’s regulatory decisions regarding Bromday are inconsistent in comparison with other products. CDER does not agree with this assertion. The Center evaluates each product on a case-by-case basis, and regulatory decisions reflect the nature of the product, the intended use, and the safety risks, among other factors. The agency’s decisions regarding other products are not an appropriate subject for consideration

ISTA Submission at 11-12 and Exhibit B (contending that “FDA has approved numerous other ophthalmic products that raise the same purported safety issues CDER believes warrant denial of Supplement 15”).

CDER intends to treat ISTA’s bromfenac products the same as similarly situated post-surgical ophthalmic products. Prior to its consideration of ISTA’s Supplement 15, it was CDER’s understanding that, as a matter of “best practices” in ophthalmology, practitioners did not prescribe a single bottle of eyedrops to be used in both eyes in a post-operative setting. CDER recently has begun to take steps to address its concern about the cross-contamination risk associated with such use. For example, the labeling for Nevanac (nepafenac ophthalmic suspension) 0.1% has been revised to explain that a single bottle should not be used to treat more than one eye in a post-operative setting. Additionally, a fill size sufficient to treat two eyes likely may be acceptable for certain ophthalmic products. For example, all of the products ISTA claims FDA has not treated similarly to Bromday are indicated for allergic conjunctivitis, which is not a post-surgical indication and is associated with a longer course of treatment (up to six weeks). CDER’s current view is that these factors make a larger fill size appropriate for such products, but the Center plans to obtain input from the DODAC on this issue at the February 2012 meeting.
in these proceedings. Indeed, information about other products was excluded from consideration at the Avastin hearing in June, and your recent decision in that matter noted that:

Issues with respect to FDA action on other products are not relevant to this proceeding. Each decision...must be made on its own merits. If the decision with respect to another product is in error, that would not justify continuing that error with respect to [this product]. See Edison Pharm. Co. v. Food and Drug Admin., 600 F.2d 831, 842 (D.C. Cir. 1979). Moreover...as a practical matter, it would not be possible to evaluate the different circumstances associated with decisions with respect to other products in the context of this or any hearing.  

For those reasons, FDA has “consistently rejected attempts to bring evidence with respect to decisions on other products into hearings,”24 and it should not deviate from that position here.  

Further, at the DODAC meeting on February 27, 2012, CDER will obtain the advice of the DODAC regarding not only bromfenac, but also similarly situated ophthalmic products. In CDER’s view, the DODAC is best positioned to consider cross-contamination risk issues for these products because of its specialized expertise, and because an advisory committee meeting is a more appropriate forum for the consideration of safety issues affecting multiple products and sponsors than this proceeding, which is limited to ISTA’s Supplement 15.

IV. Request for Opportunity to Respond to ISTA’s Submission

Because CDER recommends deferral of action on ISTA’s hearing request, we do not provide a proposed order or substantive analysis of the request here. However, if you determine that you cannot defer action on ISTA’s hearing request, CDER asks for an opportunity to provide a comprehensive written response to ISTA’s allegations before you act.


In that response, CDER would address, among other points, the scope of the agency’s authority to consider medication errors in assessing the safety of a drug, including the fact that the agency’s authority is not limited to requesting or requiring labeling changes. 25 CDER also would expect to explain that the burden of proof to establish the safety of its proposed drug product lies with ISTA. In its submissions to the agency, ISTA contends that there is no cross-contamination risk associated with the larger presentation of its product proposed in Supplement 15. However, the company has not provided any data or other information to support that assertion. 26 The statute and FDA regulations place the burden of proof squarely on the party contending that a proposed drug product is safe 27 -- namely, ISTA.

Thank you very much for your consideration.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

25 ISTA Submission at 16-17 (asserting that the FDCA “prohibits FDA from assuming in its safety calculus that physicians or patients will fail to adhere to the instructions in [a] drug’s labeling” and that Congress directed FDA to address drug misuse “though label warnings in lieu of refusing approval”). For example, FDA recently determined that an ampule presentation of esmolol hydrochloride was unsafe based on serious adverse events resulting from medication errors that were not, in the agency’s view, sufficiently mitigated by labeling changes. Determination that BREVIBLOC (esmolol hydrochloride) Injection, 250 mg/mL, 10 mL Ampule, Was Withdrawn From Sale for Reasons of Safety or Effectiveness, 75 Fed. Reg. 24710 (May 5, 2010). The medication errors included mix-ups between the ampule and the ready-to-use vial presentations, and dilution errors (failure to dilute or dilution calculation mistakes) with the ampule product.

26 Aside from ISTA’s argument that an absence of AERS reports is equivalent to an affirmative finding of safety, which is erroneous for the reasons noted above, the company’s brief raises only legal issues, which are not appropriate for consideration in a formal evidentiary public hearing before the agency. 21 CFR 12.21(a), 12.24(b)(1) and (e), and 314.200(g).

27 21 USC 355(d); 21 CFR 314.125(b) and 314.200(d).
cc: Gerald F. Masoudi, Counsel to ISTA
    Mark Raza
    G. Matthew Warren