



N A S T E C H

PHARMACEUTICAL COMPANY INC.

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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

October 13, 2005

Re: Comments on Citizen Petition
Docket No. 2005P-0360/CP1

Nastech Pharmaceutical Company, Inc. ("Nastech") submits these comments in response to the Citizen Petition (the "petition") filed by Foley & Lardner LLP, Docket No. 2005P-0360/CP1, which requests that FDA not approve any Abbreviated New Drug Application ("ANDA") for a salmon calcitonin ("sCT") nasal spray drug product citing Miacalcin sCT Nasal Spray ("Miacalcin") as the reference listed drug ("RLD") unless the ANDA satisfies certain conditions listed in the petition.

Nastech has submitted ANDA 76-979 for its chemically synthesized sCT Nasal Spray citing Miacalcin (also a chemically synthesized drug) as the RLD. FDA has notified Nastech that the ANDA was received pursuant 21 CF.R. § 314.101(b)(2), signaling that it is suitable for substantive review.

FDA should promptly deny the petition. As discussed in more detail below, the petition would require the submission of data and information which are not scientifically or medically necessary to demonstrate that Nastech's sCT nasal spray is safe and effective, and which cannot lawfully be required under the applicable law and regulations. The failure to deny this petition promptly will deprive consumers and their physicians of a safe and effective competitor to the RLD and other marketed sCT products.

2005P-0360

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Immunogenicity Data Are Not Necessary to Establish “Sameness”

The petitioner is correct that an ANDA applicant must demonstrate that its drug product contains the same active ingredient as the RLD. However, the assertion that an applicant for an ANDA for sCT cannot demonstrate sameness without providing data on immunogenicity is not correct.

FDA has repeatedly stated that conformity with standards such as the United States and European Pharmacopoeias and FDA’s Guidances on Chemistry, Manufacturing, and Controls to characterize the products in question will ordinarily be sufficient to demonstrate sameness.¹ In the case of sCT, the adequacy of such physicochemical characterization by amino acid profile testing and potency by bioassay to determine the identity and strength of a sCT drug substance is further evidenced by the sCT monograph in the European Pharmacopoeia,² and by the imminent sCT monograph in the United States Pharmacopoeia.³ As FDA itself stated recently, sCT has a “relatively simple structure (it has only a limited secondary structure – a single disulfide bond)” and therefore “lends itself to physicochemical structural characterization.”⁴ Accordingly, conformity with EP and proposed USP standards for sCT provides adequate proof of sameness. In addition, FDA’s Guidance for Industry on the Submission of Chemistry, Manufacturing, and Controls for Synthetic Peptide Substances provides detailed information on the characterization and proof of structure and other aspects of the manufacture of synthetic peptides, including

¹ See e.g., Preamble to Final Rule, Abbreviated New Drug Regulations, 57 Fed. Reg. 17,950, 17,959 (Apr. 28, 1992); Letter from Dennis Baker, Associate Commissioner for Regulatory Affairs to Donald O. Beers, et. al. at 2-3 7-9, 14-15 (Feb. 15, 2002); Letter from Kathryn C. Zoon, Ph.D., Director, Center for Biologics Evaluation and Research and Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research to Richard J. Meader, Vice President, Regulatory and Quality Affairs, McGaw, Inc. at 4-5 (Jul. 25, 1996).

² European Pharmacopoeia 5.0, 01/2005:0471. pp. 1148-1149, Calcitonin (Salmon)

³ United States Pharmacopoeial Forum, Vol. 31, No. 4, Calcitonin Salmon, p. 1036; Calcitonin Salmon Nasal Solution, p. 1178 (USP 29 Supplement 2, effective August 1, 2006)

⁴ Letter from Steven K. Galson, M.D., M.P.H., Acting Director, Center for Drug Evaluation and Research to Nancy L. Buc and Carmen M. Shepard at 8 (Aug. 12, 2005).

bioassays for potency.⁵ When the RLD is used as the reference standard, following the Guidance offers further confirmation of sameness.

Bone Resorption Data Are Not Necessary to Establish “Sameness”

The suggestion that bone resorption data are necessary to prove “sameness”⁶ also ignores the physicochemical characterization and bioassay criteria noted above.

Evaluation of Impurities Is Not Relevant to “Sameness”

The petition asserts that differences in the spectrum of impurities would undermine sameness and might affect the overall response to the product, and implies that differences in impurities might somehow cause differences in immunogenicity. The points it makes in support of these arguments, as well as the arguments themselves, are erroneous.

First, FDA’s regulations and practice deal with safety issues raised by impurities as a CMC issue, not as a sameness issue.⁷ FDA’s review of the impurities profile as part of its review of the CMC section of an ANDA is the appropriate means of assessing whether the impurities present in a product raise safety issues.

Second, there is no scientific reason (and petitioner provides none) to think that two sCTs which both meet pharmacopoeial standards and for which one is the reference drug for the other for CMC purposes would have any meaningful differences in immunogenicity.

⁵ FDA, Guidance for Industry for the Submission of Chemistry, Manufacturing, and Controls Information for Synthetic Peptide Substances at 2-3, 9 (Nov. 1994).

⁶ Petition at 6

⁷ See, Preamble to Final Rule, Abbreviated New Drug Regulations, 57 Fed. Reg. at 17,959; FDA, Guidance for Industry, ANDAs: Impurities in Drug Substances at 1 (Nov. 1999).

Third, the petition creates a red herring by noting differences between the RLD and human calcitonin, which has nothing to do with whether one sCT is the same as another sCT. Likewise, whether two erythropoietin products are similarly antigenic is also irrelevant to whether two sCTs are the same.

A Preservative Does Not Determine Bioavailability

The petition argues that different preservatives might affect bioavailability and therefore bioequivalence of sCT products. The statute and the regulations require a showing of bioequivalence, so if bioequivalence has been shown, as it has for Nastech's sCT with respect to the RLD, any theoretical concern about the effect of a preservative has been eliminated.

The preservative used in Nastech's product appears on FDA's list of inactive ingredients and is widely used in similar or higher concentrations in nasal spray and nasal solution drug products and several other dosage forms.

Other Safety Issues

The petition speculates that leachates, contaminants, degradants, inactive ingredients, as well as impurities, could affect the safety profile of a sCT active ingredient. The petition provides no information to support its speculation, but in any case, these issues are all part of the CMC review which FDA conducts during the review of Nastech's ANDA.

Conclusion

This Citizen Petition is clearly an effort to delay approval of a generic salmon calcitonin product in order to prevent competition in the marketplace with previously approved calcitonin products for osteoporosis. The petition should be denied post haste, so that there will be no delay to approval of Nastech's ANDA. Nastech wishes to emphasize that FDA is under no legal

obligation to withhold approval of an otherwise ready-to-go ANDA to allow time to deal with petitions such as this. Thus, Nastech's ANDA should be approved as soon as it is ready, whether or not FDA is prepared to respond to this meritless petition.

Sincerely yours,

A handwritten signature in black ink that reads "Gordon Brandt MD". The signature is written in a cursive, flowing style.

Gordon Brandt, M.D.
Executive Vice President, Clinical Research and Medical Affairs,
Nastech Pharmaceutical Company, Inc.

cc: Gary J. Buehler, R.Ph.
David Orloff, M.D.
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