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VIA FEDERAL EXPRESS

Dockets Management Branch (HFA 305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

**Re: Citizen Petition, Docket Number 2005P-0360
Requirements for Applications for Salmon Calcitonin Products
Response to Nastech Pharmaceutical Company, Inc.'s Comments**

Dear Sir or Madam:

The undersigned submits this letter in response to the comments filed by Nastech Pharmaceutical Company, Inc. ("Nastech") on October 14, 2005, regarding CP Docket 2005P-0360.

Nastech has indicated that they submitted an Abbreviated New Drug Application ("ANDA") for chemically synthesized salmon calcitonin ("sCT") nasal spray, citing Miacalcin[®] as the reference listed drug ("RLD"). Nastech also stated that the Citizen Petition should be denied based on Nastech's assertion that the Petition would require the submission of data and information which is not scientifically or medically necessary to demonstrate that the Nastech product is safe, effective and equivalent to the RLD. The original Petition requested that any applicant for sCT nasal spray, whether that be via an ANDA or 505(b)(2) NDA ("505(b)(2)") be required to demonstrate: (1) the active ingredient described in the ANDA or 505(b)(2) is the "same" as that of the Miacalcin[®] active ingredient; (2) the ANDA or 505(b)(2) NDA contains appropriate bioequivalence data using plasma concentration of sCT and a suitable bioassay that bridge the ANDA or 505(b)(2) product to Miacalcin[®] (unless the application contains new clinical and/or preclinical data to support differences between the ANDA or 505(b)(2) product and Miacalcin[®]); and (3) the ANDA or 505(b)(2) NDA contains documented safety comparability to Miacalcin[®], including immunogenicity testing generated through a

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clinical study. These comments to the Nastech response are being submitted because Nastech has misinterpreted the concerns cited in the Petition and essentially summarily dismissed the central issues raised in the Petition.

Nastech Assertion: Immunogenicity Data Are Not Necessary to Establish “Sameness”

Nastech titled its responsive assertion as stated above. However, the Petitioner’s title was: “Proof of Sameness of the Active Ingredient and Adequacy of Bridging Information to Tie a Generic Product to the Safety and Efficacy of the RLD.” Nastech has misinterpreted the point made in the original Petition and by doing so has failed to address the underlying issue – that is, it is the ANDA applicant that must establish “sameness” of the active ingredient in order for the product provided for in the ANDA to be eligible for submission and approval as an ANDA. To support its assertion, Nastech cites FDA statements in the preamble to the final ANDA regulations regarding conformity to standards such as the United States and European Pharmacopeia’s and FDA’s Guidances on Chemistry, Manufacturing and Controls (“CMC”) to characterize the product in question and asserts that it will ordinarily be sufficient to demonstrate sameness. It is interesting to note however, that Nastech neglected to cite the next sentence in the preamble to the ANDA regulations that states: “However, in some cases, FDA may prescribe additional standards that are material to the ingredient’s sameness.”¹ The issues surrounding the establishment of sameness of sCT are more complex than for other drugs. Reference is made to the original Petition which outlined issues that are critical to establishing the sameness of the active ingredient.

Specifically, in response to Nastech’s comments, first, the European Pharmacopeia (“EP”) has no legal standing in the US – for approval of products or demonstration of “sameness,” so Nastech’s point seems out of context. The EP monograph may be somewhat helpful in establishing some evidence of “sameness,” however, for products such as generic sCT that present immunological concerns and technical difficulties in establishing bioequivalence, mere reference to a monograph standard, especially a European one, does not address such concerns.

Second, the United States Pharmacopeia (“USP”) and “CMC” Guidances do not address the “adequacy of bridging information to tie a generic product to the safety and efficacy of the RLD.” This “adequacy” is a decision that must be made by the FDA reviewers in the Center for Drug Evaluation and Research in the Office of Generic Drugs, often after consultation with the reviewers in the Office of New Drug Evaluation. However, since Nastech has cited the USP, it may be interesting to consider a position paper that the USP developed entitled “*Equivalence Studies for Complex Active*

¹ Preamble to Final Rule, Abbreviated New Drug Regulations, 57 Fed. Reg., 17950, 17959 (Apr. 28, 1992.)

Ingredients and Dosage Forms.” Dr. Roger Williams, Executive Vice President and Chief Executive Officer for the USP (and former Director, Office of Generic Drugs), filed this paper to the Division of Docket Management on March 15, 2005. The Williams paper specifically mentions calcitonin as an example, so it is appropriate to mention it herein. In his own summary of the paper, Dr. Williams stated:

USP provides public monographs, which are standards to which all manufactured ingredients and products should conform, and which constitute a starting point for follow-on manufacturers. Monographs provide a baseline set of quality requirements that apply to all manufacturers. However, it is recognized that substantial additional one-time characterization studies may be needed, on a case by case basis, to document equivalence.

Dr. Williams also stated in his cover letter of March 15, 2005:

A combination of risk-based approaches used by regulatory agencies, by industry, and by the pharmacopeia can assure that therapeutic protein ingredients and products will be safe, effective, and of a consistent quality from batch to batch or from producer to producer.

From the referenced paper itself: Under Matrix of Peptides and Proteins:

Peptides: Peptides consist of ...Examples include... calcitonins... Three major synthetic strategies for a peptide are: 1) chemical (both solid-phase and solution-phase); 2) biochemical (e.g. fermentation); and 3) rDNA technology.... Despite the small number of amino acid residues, peptides may have significant structural characteristics, which presumably can impact clinical performance. ...Although physicochemical characterization and purity analyses are more straightforward than for proteins, these methods may still not be sufficient to predict biologic toxicity and immunogenicity.

The citations from Dr. Williams are, in essence, a different articulation of the concerns raised in the Citizen Petition Docket Number 2005P-0360. The characterization of Nastech’s drug substance and drug product, described in ANDA 76-979, must include characterization of the protein active ingredient and the drug product in order to demonstrate “sameness” to the RLD. The adequacy of this characterization must be considered by FDA staff before approval of an ANDA or 505(b)(2) because it ties the generic drug to the established safety and efficacy of the RLD.

In addition, Dr. Williams has stated that the industry should use a risk-based approach in assuring that drugs are safe and effective. Extending this thought, it is prudent that Nastech evaluate their product for immunogenicity before marketing it to the public. The Petitioner is of the opinion that any sCT ANDA or 505(b)(2) product should have documented safety, comparable to Miacalcin[®], including immunogenicity testing by clinical trials. If Nastech summarily dismisses this statement, they should reconsider the points in the original Petition and additional explanation in this letter and provide substantive data in their application to address the potential safety issues that arise out of immunogenicity concerns. The health and safety of patients are of paramount importance and Nastech is compelled to address immunogenicity concerns. I want to emphasize that the Petitioner does not request that the Nastech ANDA be withheld from approval – only that FDA consider the points in the petition to assure that the Nastech data provides all that is necessary to establish “sameness” of the active ingredient, including immunogenicity information relative to establishing the same safety and efficacy to the RLD, the innovator product, Miacalcin[®] nasal spray.

The RLD that has been administered to patients for over 10 years is an entire formulation and not the drug substance alone. The entire finished drug product administered to patients consists of drug substance, excipients in the formulation, impurities, degradation products, aggregates and contaminants, including any resulting from contact with package/metered dose nasal pump. It cannot be assumed that a generic for the RLD, that has the same drug substance, but not necessarily the same impurities and degradation products, and aggregates and components in the drug product formulation and packaging materials will have the same safety and efficacy profile as the RLD. Consider a hypothetical synthetic process for manufacturing sCT – perhaps similar to the one that Nastech uses to manufacture their drug substance. The n-1, n-2, etc. impurities that may occur in a synthetic peptide manufacturing process may or may not be very different in immunogenicity from the Novartis manufacturing process used to establish the historical safety and efficacy profile of the RLD. However, if that very same n-1 impurity also has a protecting group (protecting groups are used when synthetically manufacturing peptides), then there is the potential to have a very different immunogenic profile from the RLD. Likewise, branched peptides, racemic mixtures, internal deletion sequences and dimers that may be part of the final generic sCT, may be the cause of differing immunogenic profiles compared to the RLD. All chemically synthesized peptides will contain significant amounts of these contaminants. For example, if only 1% racemization occurs at each added residue in a synthetic peptide, then in a 32 amino acid peptide such as sCT, only 68% of the molecules will have the correct stereochemistry. The spectrum of possible contaminants in peptide molecules made by chemical synthesis has been well documented (see attachment, for example, from a USP educational conference, 2003.)

Moreover, depending on the method of synthesis, the amounts and ratios of the different possible contaminants will vary. The RLD drug was and is manufactured by a synthetic process, documented in its NDA, and supplemented, as appropriate, whenever CMC changes occurred, throughout years of marketing. FDA is aware of the CMC technical information for this RLD, and the resulting efficacy and safety profile of the marketed RLD (drug product). Nastech has also filed or referenced a synthetic process and associated CMC information for their ANDA, and has presumably identified impurities, contaminants, and degradants. If Nastech were able to exactly duplicate the Novartis process, there would be no need for this petition. However, the Petitioner is assuming that there may be differences in the manufacturing process and thus differences in impurities, contaminants and degradants. Such differences in impurities, contaminants and degradants must be considered for their impact on safety (immunogenicity) and efficacy (titer and presence of neutralizing antibodies) of a marketed generic product. Even minor contaminants have the potential to be hyper-immunogenic. Thus, for example, citing the *Journal of Immunology*: a contaminant present at low abundance ($\leq 1\%$) in the synthesis of an 8 amino acid peptide was found to be highly immunogenic, and Purcell *et al* conclude that "this study not only highlights the potential of impurities to act as surrogate immune targets, but previous studies of ours (references) and others (references) suggest that other spontaneously occurring modifications may occur in peptide ligands during processing, storage, or administration, which may lead to unwanted and potentially hazardous immune responses" (Purcell *et al. J. Immunol.* 1998, 160: 1085-1090).

The WARNINGS in the package insert ("PI") for the RLD, include information about anaphylactic shock and in one case, death due to anaphylaxis (attributed to preservative/injection formulation). The historical safety profile and the current safety profile for the RLD (including Novartis Periodic Safety Reports) and relationship to Novartis CMC changes should be considered by FDA. It is FDA's expertise that must be drawn upon to decide whether the differences in the CMC profile of a generic drug will have the same efficacy and safety profile of the RLD. The Petitioner has considered the information listed above, and firmly believes that clinical data to evaluate immunogenicity is needed prior to approval of any generic sCT drug product, in order to establish the same profile as the RLD.

Nastech Assertion: Bone Resorption Data Are Not Necessary to Establish "Sameness"

Nastech titled its responsive assertion as stated above. However, the Petitioner's title was: "Proof of Sameness of the Active Ingredient and Adequacy of Bridging Information to Tie a Generic Product to the Safety and Efficacy of the RLD." Nastech states that they have carried out a physicochemical characterization and bioassay, and therefore bone resorption data are not necessary to establish "sameness" to the innovator. The Petitioner restates its position that only FDA has the expertise and authority to decide

upon the adequacy of Nastech's data to establish proof of sameness of the active ingredient and the adequacy of bridging information prior to approval of an ANDA. The Petitioner only asks that FDA consider the points in the Citizen Petition and this response letter in establishing the "sameness" of the active ingredient to that in the RLD and adequacy of bridging information in applications prior to approval.

Nastech Assertion: Evaluation of Impurities is Not Relevant to "Sameness"

In this section, Nastech erroneously states that "there is no scientific reason (and the 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." The Petitioner has outlined previously and states again above in great detail the numerous reasons why Nastech's assertion is neither supported by the fact nor by sound science. Yet Nastech chooses to dismiss the concern for immunogenicity of a protein or peptide based pharmaceutical, either due to the active ingredient itself, or due to the myriad of impurities, aggregates or degradation products that can result from the manufacturing and/or packaging process.

In this section, Nastech also states that "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." There is no red herring because the points in the original Petition were not intended to be all-inclusive or exactly applicable to a particular sCT ANDA or 505(b)(2) when FDA evaluates the body of evidence supporting "proof of sameness of the active ingredient and adequacy of bridging information." The first point – that salmon calcitonin is not the same as endogenous human calcitonin – merely illustrates the point that risk of immune response increases as changes to the sequence are made. Therefore, it is reasonable to expect an immune response to any sCT and its particular n-1, n-2, etc deletion contaminants. The Petitioner does not take the position that one sCT peptide, defined herein as the full-length, intact peptide, is expected to have a different immunogenic profile compared to another sCT peptide, also defined as the full-length, intact peptide. The Petitioner takes the position that different synthetic manufacturing processes result in differing arrays of peptides in the sCT drug substances being compared, and they cannot be assumed to have the same immunogenic profile.

As a separate point, the reference article regarding erythropoietin products was cited because research on the products described in the article has resulted in an increased understanding of factors that contribute to immunogenic risks. As was shown in this article, even minor CMC changes have the potential to impact immunogenicity. The Petitioner reiterates concern regarding the need for appropriate immunogenicity studies before approving a particular sCT ANDA or 505(b)(2).

Nastech Assertion: A Preservative Does Not Determine Bioavailability

In this section, Nastech asserts that a theoretical concern about bioavailability and the effect of preservative has been eliminated because Nastech has demonstrated bioequivalence to the RLD. The Petitioner agrees that demonstration of bioequivalence according to current FDA's standards would eliminate any theoretical concern about Nastech's drug product formulation. However, establishment of bioequivalence for generics to the RLD has significant technological challenges. Nastech should have used an assay that was validated to recognize only the intact sCT and not its degradation products, for its bioavailability study, or the bridge to the RLD profile will be materially flawed. Also, Nastech must formulate to 100% of labeled drug content and deliver the same dose with the same rate and extent of absorption as the RLD. It is difficult to achieve these simultaneously for this RLD, one with extremely low and variable bioavailability. However, the Petitioner agrees that Nastech need not be concerned about their drug product formulation if they have proven to the satisfaction of FDA that they are bioequivalent to the RLD.

Nastech Assertion: Other Safety Issues

In this section, Nastech asserts that the Petitioner provides no information to support the proposition that leachates, contaminants, degradants, inactive ingredients, as well as impurities, could affect the safety profile of a sCT active ingredient. Nastech further asserts that "these issues are all part of the CMC review which FDA conducts during the review of Nastech's ANDA." It is readily apparent that Nastech does not understand the points made by the Petitioner or is summarily dismissing them. The Petitioner is of the opinion that FDA has more than enough data and information, obtained through years of regulating drugs, to support that leachates, contaminants, degradants, inactive ingredients, as well as impurities have affected and will continue to affect the safety profile of many drugs. The information that FDA needs to grant the request of the Petitioner is already held within the Agency.

Conclusion

Any ANDA applicant for sCT, including Nastech, is required to provide information in its application to demonstrate that its sCT is the same as the active ingredient in the RLD. The Petitioner firmly believes that in order to establish sameness of the active ingredient in Nastech's product to that of the RLD, Nastech must provide appropriate characterization data. In addition, the Petitioner believes that bioequivalence data using plasma concentrations of sCT with a suitable assay and an immunogenicity clinical study are necessary to establish therapeutic equivalence to the RLD. Finally, Nastech asserts that the Citizen Petition is clearly an effort to delay approval of a generic sCT product in order to prevent competition in the marketplace and should be denied post haste, so that there is no delay to approval of Nastech's ANDA. That is simply not the

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case. The Petitioner believes that such information and data are required by law and regulation and are necessary to ensure that the products are the same, bioequivalent and therapeutically equivalent in the interest of public health and safety.

Respectfully submitted,

A handwritten signature in black ink that reads "David L. Rosen". The signature is written in a cursive style with a prominent initial "D".

David L. Rosen, B.S. Pharm., J.D.
Foley & Lardner, LLP