DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

AUG 12 2005

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Nancy L. Buc
Carmen M. Shepard
Buc & Beardsley
919 Eighteenth St., N.W.
Suite 600
Washington, D.C. 20006-5503

Re: Docket No. 2004P-0015/CP1

Dear Ms. Buc and Ms. Shepard:

This letter responds to your citizen petition dated January 9, 2004 (Petition), regarding recombinant salmon calcitonin nasal spray. You request that the Food and Drug Administration (FDA or the Agency) deny approval of any new drug application (NDA) for salmon calcitonin nasal spray for the prevention or treatment of osteoporosis that lacks clinical data showing efficacy in the prevention or treatment of bone fractures. Specifically, you request that Unigene Laboratories, Inc.'s (Unigene's) NDA for Fortical not be approved under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 355(b)(2)) for the prevention or treatment of osteoporosis without such fracture data. In your response to comments dated April 27, 2005, you request that the scientific issues raised by your petition be referred to an advisory committee.

We have carefully considered the issues you raise in your petition, the comments on your petition submitted by Unigene on April 11, 2005, and your April 27, 2005, response. For the reasons stated below, your petition is denied.

I. BACKGROUND

A. Section 505(b)(2) Applications[1]

Section 505(b)(2) of the Act was enacted as part of the Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman Amendments). Section 505(b)(2) provides:

> An application [may be] submitted under [section 505(b)(1)] for which the [safety and effectiveness] investigations . . . relied upon by the applicant [to support] approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted [and] shall also include [patent certifications for patents on the drug for which investigations were conducted or a method of use statement].

[1] The background on section 505(b)(2) provided in this section of the petition response is largely drawn from a more extensive discussion of 505(b)(2) applications set forth in FDA's October 14, 2003, response to several citizen petitions (2001P-0323/CP1 & C5, 2002P-0447/CP1, and 2003P-0408/CP1) concerning section 505(b)(2) issues.

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The Hatch-Waxman Amendments reflect Congress's attempt to balance the need to encourage innovation with the desire to speed the availability of lower-cost alternatives to approved drugs. With passage of the Hatch-Waxman Amendments, the Act describes different routes for obtaining approval of two broad categories of drug applications: (1) an NDA, for which the requirements are set out in section 505(b) and (c) of the Act, and (2) an abbreviated new drug application (ANDA), for which the requirements are set out in section 505(j). These categories can be further subdivided as follows:

- Stand-alone NDA—an application that contains full reports of investigations of safety and effectiveness that were conducted by or for the applicant or for which the applicant has a right of reference (section 505(b)(1));

- 505(b)(2) application—an application that contains full reports of investigations of safety and effectiveness, where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference (section 505(b)(2));

- ANDA—an application for a duplicate of a previously approved drug that contains information to show that the proposed product is identical in active ingredient(s), dosage form, strength, route of administration, labeling, quality, performance characteristics, and intended use, among other things, to a previously approved product, and for which clinical studies are not necessary to show safety and effectiveness (section 505(j)); and

- Petitioned ANDA—an application for a drug that differs from a previously approved drug product in dosage form, route of administration, strength, or active ingredient (in a product with more than one active ingredient), for which FDA has determined, in response to a *suitability petition* submitted under section 505(j)(2)(C), that clinical studies are not necessary to show safety and effectiveness (section 505(j)).

A 505(b)(2) application shares characteristics of both an ANDA and a stand-alone NDA. Like a stand-alone NDA, a 505(b)(2) application is submitted under section 505(b)(1) of the Act and approved under section 505(c). As such, it must satisfy the requirements for safety and effectiveness information. A 505(b)(2) application is similar to an ANDA as well because it may rely on the FDA finding that the listed drug it references is safe and effective as evidence in support of its own safety and effectiveness. However, although an ANDA is generally required to duplicate an innovator product (with a few limited exceptions)—and an ANDA therefore may not include new clinical safety or effectiveness information to support approval—a 505(b)(2) application often describes a

drug with substantial differences from the listed drug it references. Accordingly, it must support those differences with appropriate safety and effectiveness information. FDA's long-standing interpretation of section 505(b)(2) is intended to permit the pharmaceutical industry to rely, to the greatest extent possible under the law, on what is already known about a drug. Our approach is to use the 505(b)(2) drug approval pathway to avoid requiring drug sponsors to conduct and submit studies that are not scientifically necessary. The conduct and review of duplicative studies would (1) divert industry resources that could be used to undertake innovative research, (2) increase drug costs, (3) strain FDA review resources, and (4) slow the process for drug approval with no corresponding benefit to the public health. In addition, the conduct of duplicative studies raises ethical concerns because it could subject human beings and animals to medically or scientifically unjustified testing. The 505(b)(2) pathway permits sponsors and the Agency to determine what studies are necessary to support the approval of a new aspect of a drug. It then allows sponsors to target drug development resources to studies needed to support the proposed difference or innovation from the previously approved drug product on which it seeks to rely (see 21 CFR 314.54(a) ("[A 505(b)(2)] application need contain only that information needed to support the modification(s) of the listed drug")).

In response to many requests from industry and based on accumulated Agency experience in applying section 505(b)(2) of the Act, in October 1999 we published a draft guidance for industry entitled *Applications Covered by Section 505(b)(2)* (the 505(b)(2) Draft Guidance). The 505(b)(2) Draft Guidance (at 2 to 3) states that an applicant seeking approval under section 505(b)(2) can rely on a combination of published literature, its own clinical studies, and/or the Agency's finding of safety and effectiveness for a listed drug. It also notes that a 505(b)(2) application can be submitted for different types of applications, including for a new chemical entity, or for a change to a previously approved drug (e.g., new dosage form, strength, or route of administration) (id. at 3 to 5). In particular, the Draft Guidance states that a 505(b)(2) application may be accepted for a drug product containing an active ingredient derived from recombinant technology where clinical investigations are necessary to show that the active ingredient is the same as an active ingredient in a listed drug (id. at 5).

When a sponsor of a 505(b)(2) application seeks to rely on a finding of safety and effectiveness for a previously approved drug product, it must establish its basis for relying on a previous approval. Typically, a 505(b)(2) applicant can establish this basis by conducting one or more bioavailability/bioequivalence (BA/BE) studies to bridge its proposed product to the previously approved product. The 505(b)(2) applicant also must provide any additional data necessary to support the change for which the applicant is seeking approval. In the case of a change from a synthetic form of an active ingredient to a recombinant form, we might require pharmacodynamic and other studies to establish the sameness of the active ingredient, in addition to the BA/BE studies traditionally required to bridge the proposed drug product to an approved one.

B. Miacalcin Nasal Spray and Fortical

On August 17, 1995, we approved Novartis Pharmaceuticals Corporation's (Novartis's) NDA (20-313) for Miacalcin (calcitonin-salmon) Nasal Spray (Miacalcin NS) for the treatment of postmenopausal osteoporosis in females greater than 5 years postmenopause with low bone mass relative to healthy premenopausal females. The active ingredient in Miacalcin NS is a synthetic version of salmon calcitonin.

The development of Miacalcin NS preceded FDA's issuance, in 1994, of a draft guidance entitled *Guidelines for Preclinical and Clinical Evaluation of Agents Used in the Prevention or Treatment of Postmenopausal Osteoporosis* (the Osteoporosis Draft Guidelines). For approval of nonestrogen drugs used to treat postmenopausal osteoporosis, the Osteoporosis Draft Guidelines recommend that a sponsor provide evidence that its drug reduces the risk for vertebral fracture after 3 years of treatment. Beginning with our approval of Fosamax (alendronate sodium) in September 1995, all drugs approved for the treatment of postmenopausal osteoporosis have been shown to reduce the risk for fracture at 3 years. Because the clinical studies for Miacalcin NS preceded the Osteoporosis Draft Guidelines, the types of studies on which Miacalcin NS was approved differed from those for Fosamax and other subsequently approved osteoporosis drugs. As a result of these differences in studies conducted, Miacalcin NS's indication also differs from that of subsequently approved nonestrogen drugs for the treatment of postmenopausal osteoporosis; Miacalcin NS is approved only for a subset of the postmenopausal osteoporosis indication.

On August 12, 2005, we approved Unigene's 505(b)(2) application for Fortical, a salmon calcitonin nasal spray product. The Fortical NDA, submitted in 2003, relied in part on the finding of safety and effectiveness for Miacalcin NS. Fortical and Miacalcin NS differ in two principal ways: (1) the active ingredient in Fortical, salmon calcitonin, is manufactured through recombinant genetic technology, whereas the salmon calcitonin in Miacalcin NS is manufactured through chemical synthesis; and (2) Fortical contains different types and amounts of excipients. The Fortical NDA included, among other things, data from a clinical study demonstrating that the pharmacodynamic effects of Fortical on bone resorption are noninferior to those of Miacalcin NS and a study demonstrating that the bioavailability of Fortical is comparable to that of Miacalcin NS. On the basis of these and other data, including physicochemical characterization, Unigene demonstrated that Fortical contains the same active ingredient as Miacalcin NS and meets the requirements for approval under section 505(b)(2) of the Act.

II. DISCUSSION

A. Fracture Data Issues

You state that a 505(b)(2) application that "relates back" to the 505(b)(1) NDA for Miacalcin NS must contain both (1) two years of bone mineral density data and (2) at least the minimal fracture data that you claim FDA required for Miacalcin NS. In support of your argument, you state that FDA no longer approves nonestrogenic products

intended to prevent or treat osteoporosis on the basis of clinical trials demonstrating an effect only on bone mineral density and other markers. You state that, instead, the Agency has typically required 3 years of fracture data as proof of efficacy for an osteoporosis treatment indication (Petition at 3). For the reasons stated below, we do not agree that fracture data are essential to the approval of a 505(b)(2) application that relies on the finding of safety and effectiveness for Miacalcin NS, in particular the 505(b)(2) application for Fortical.

We did not require fracture data for the approval of Miacalcin NS. Rather, the approval was based on data showing that the drug increased bone mineral density to a greater degree than did placebo in postmenopausal women with low bone mass. The *Indications and Usage* section of the Miacalcin NS package insert states that "[t]he evidence of efficacy [of the drug] is based on increases in spinal bone mineral density observed in clinical trials."

However, even if we had required fracture data for the approval of Miacalcin NS, such data would not have been required for the approval of Fortical. We had previously found that Miacalcin NS is safe and effective for the treatment of postmenopausal osteoporosis in females greater than 5 years postmenopause with low bone mass relative to healthy premenopausal females. Because the Fortical NDA relied on our findings of safety and efficacy for Miacalcin NS for the same indication, Unigene was required to submit data necessary to (1) establish that the findings of safety and efficacy for Miacalcin NS are relevant to Fortical (i.e., that they have the same active ingredient and comparable bioavailability) and (2) evaluate and establish the safety and efficacy of any differences in Fortical from Miacalcin NS. There was no need for the Fortical NDA to contain data on clinical endpoints (i.e., fracture rates) because such data were not necessary to (1) establish the sameness of the active ingredient or to otherwise bridge to the Miacalcin NS NDA or (2) support any differences between the Fortical and Miacalcin NS products.

You state that in November 1994, FDA's Endocrinologic and Metabolic Drugs Advisory Committee reviewed data from the first 2 years of the 5-year Prevent Recurrence of Osteoporotic Fractures (PROOF) study on the effectiveness of Miacalcin NS in preventing osteoporotic fractures (Petition at 6, 8). That is incorrect. Data from the PROOF study were not yet available at the time of the November 1994 advisory committee meeting. In fact, those data were not available until after we approved Miacalcin NS in August 1995. The advisory committee did review some fracture data from two earlier studies, but these data were not meaningful because the studies from which they were derived were underpowered for evaluation of fracture risk. The advisory committee unanimously concluded that the changes in bone mineral density demonstrated in the clinical trials were sufficient to establish the clinically important efficacy of nasal calcitonin, and the committee voted 6 to 2 for the approval of Miacalcin NS on the basis of the bone mineral density data presented (two members wanted to await the completion of the PROOF study). As stated above and as the approved labeling reflects, our decision to approve Miacalcin NS was not based on fracture data but on the data regarding the effect of Miacalcin NS on bone mineral density.

You state that the final results of the PROOF study were disappointing in that although the 200 IU dose of calcitonin nasal spray reduced the risk of fractures, neither the 100 IU dose nor the 400 IU dose did so, and the latter dose was the only one that resulted in an increase in bone mass density.[2] Nevertheless, you conclude that because the 400 IU group fracture rate was not different from the placebo group rate, the PROOF study demonstrates clearly that an increase in bone mineral density cannot be a surrogate for fracture rate (Petition at 6). We disagree with your characterization of the PROOF results.

Our assessment of the completed PROOF study is that it did not support the approval of a salmon calcitonin nasal spray for the prevention of osteoporotic fractures in postmenopausal women. It is not our position that the PROOF data show that Miacalcin NS does not reduce vertebral fracture risk. Rather, we conclude that, because of the findings you note and other reasons stated in the Colman article to which you refer, the data are inadequate to permit a definitive conclusion on the existence or magnitude of fracture risk reduction associated with Miacalcin NS treatment in postmenopausal women with osteoporosis.[3]

You state that, based on the results of clinical trials of fluoride, etidronate, injectable calcitonin, and nasal spray calcitonin, it is clear that for nonestrogen drugs, improvements in bone mineral density do not necessarily predict a beneficial effect on fracture rates. You claim that bone mineral density data that are not corroborated by fracture data do not provide adequate evidence of efficacy to support approval of a 505(b) application.[4] Therefore, you maintain that approvals of osteoporosis drugs must rest on fracture data, not just bone mineral density data. Moreover, you state that the sponsors of Fosamax (alendronate), Actonel (risedronate), and Evista (raloxifene) presented data showing that their products both improved bone mineral density and reduced the rate of bone fractures (Petition at 7).

These arguments are misplaced and provide no basis for concluding that fracture data are necessary for the approval of Fortical. As stated in section I.B of this response, we approved Miacalcin NS on the basis of studies conducted before the issuance in 1994 of the Osteoporosis Draft Guidelines, which recommend (for nonestrogens) studying the

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[2] Petition at 6 and footnotes 22 and 23, citing Colman, E., R. Hedin, J. Swann et al., A Brief History of Calcitonin, *Lancet* 2002; 359:885-886; and Chestnut III, C.H., S. Silverman, K. Adriano et al., A Randomized Trial of Nasal Spray Salmon Calcitonin in Postmenopausal Women with Established Osteoporosis: The Prevent Recurrence of Osteoporotic Fractures Study, *Am J Med* 2000, 109:267, 272-73.

[3] You quote a statement in the Colman article in *The Lancet* suggesting that ". . . the fact that bone mineral density data and fracture risk trends did not correlate in [the PROOF] study is consistent either with a true absence of efficacy of nasal calcitonin to reduce fracture risk or with a conclusion that bone mineral density is not a valid surrogate for bone quality and fracture risk for this agent. Either way, the data are puzzling" (Petition at 6 to 7, quoting Colman at 886). This statement, by an FDA medical officer, was a commentary on the usefulness of the PROOF data, not on the evidence that was the basis for the approval of Miacalcin NS. In any case, the article was intended to provide information to physicians and patients on the treatment of osteoporosis and did not represent the official position of FDA on any matter before the Agency.

[4] Petition at 7 and footnote 28, citing the Osteoporosis Draft Guidelines at 7, 9.

effect of a drug on the rate of fracture occurrence to obtain approval for the treatment or prevention of postmenopausal osteoporosis. We approved Fosamax, Actonel, Evista, Forteo (teriparatide), and Boniva (ibandronate sodium) on the basis of studies conducted in accordance with the Osteoporosis Draft Guidelines. The NDAs for these drug products were approved under section 505(b)(1) and did not rely in any way on a previous finding of safety and effectiveness for Miacalcin NS. However, the Fortical NDA is a 505(b)(2) application referencing the findings of safety and effectiveness for Miacalcin NS and seeking approval for the same indication. We have no reason to believe that Miacalcin NS is no longer safe and effective for the indication for which it was approved. Moreover, as discussed in section II.B of this response, Unigene provided data from a pharmacodynamic study adequate to establish that Fortical and Miacalcin NS have the same active ingredient and other data necessary to ensure that Unigene could rely on the safety and efficacy findings for Miacalcin NS. Consequently, it was not necessary for the Fortical NDA to include clinical data on fracture rates to establish its effectiveness.

You state that fracture data are especially imperative regarding the approval of Fortical because its active ingredient, recombinant salmon calcitonin, is not identical to Miacalcin NS's active ingredient, synthetic salmon calcitonin. Thus, you state that one cannot assume that the properties of recombinant calcitonin are identical to those of the synthetic salmon calcitonin or that recombinant calcitonin is as safe and effective as the synthetic product (Petition at 3 and 8).

Under the 505(b)(2) Draft Guidance, an applicant may submit an NDA under section 505(b)(2) of the Act when the proposed drug product contains an active ingredient derived from recombinant technology and when clinical investigations are necessary to show that the active ingredient is the same as an active ingredient in a listed drug. This is exactly the situation with the 505(b)(2) application for Fortical. The active ingredient in Fortical, salmon calcitonin, is derived from recombinant technology. As explained in greater detail below, in addition to providing a physicochemical characterization of its recombinant salmon calcitonin, Unigene has conducted clinical investigations to show that the salmon calcitonin in Fortical is the same as the salmon calcitonin in the listed drug, Miacalcin NS. Consequently, the fact that Fortical is a recombinant salmon calcitonin drug product while Miacalcin NS is a synthetic product provides no basis for prohibiting the Fortical NDA from relying on the finding of safety and effectiveness for Miacalcin NS and requiring that the Fortical NDA include fracture data to establish effectiveness. Moreover, as discussed in section II.B of this response, Unigene provided pharmacodynamic, bioavailability, toxicological, and other data in its 505(b)(2) application demonstrating that Fortical meets the statutory standards for approval.

B. The Fortical NDA

You state that the Fortical NDA is apparently a 505(b)(2) application that contains one study on Fortical itself and otherwise relies on FDA's determinations regarding Miacalcin NS. You claim that the single study on Fortical is inadequate to meet the following burdens under section 505(b)(2) of the Act: (1) showing that it is scientifically

permissible to reach the same conclusions about the proposed drug as FDA previously reached for the referenced drug; and (2) showing that, despite differences between the proposed drug and the referenced drug, the proposed drug is nevertheless safe and effective (Petition at 7). You repeat your claim that the PROOF data on fractures confirmed the bone mineral density data and played an essential part in the approval of Miacalcin NS. You note that, in contrast, there are no fracture data on Fortical, so you conclude that the data on Fortical do not provide proof of the effectiveness of the drug (id. at 8). For the reasons stated below, your claim that the data offered in support of the 505(b)(2) application for Fortical are inadequate is incorrect.

1. Sameness of Active Ingredients

We approved Fortical in accordance with our policy on 505(b)(2) applications, under which we may accept a 505(b)(2) application for a drug product containing an active ingredient derived from recombinant technology where clinical investigations are necessary to show that the active ingredient is the same as an active ingredient in a listed drug. To obtain the approval of Fortical, Unigene provided evidence demonstrating that (1) the active ingredient in Fortical is that same as that in Miacalcin NS and that, therefore, the Fortical NDA could rely for approval on the finding of safety and effectiveness for Miacalcin NS, and (2) the differences in Fortical from Miacalcin NS do not adversely affect Fortical's safety or effectiveness.

Salmon calcitonin's relatively simple structure (it has only a limited secondary structure—a single disulfide bond) lends itself to physicochemical structural characterization. The active ingredient in Fortical, salmon calcitonin, is derived from recombinant technology; however, its primary and secondary structures are identical to those of naturally occurring salmon calcitonin and likewise to those of the active ingredient of Miacalcin NS, a synthetic salmon calcitonin. In addition, the tertiary structures of the three versions of salmon calcitonin are indistinguishable. Moreover, Unigene conducted clinical investigations to demonstrate that the salmon calcitonin in Fortical (1) has the activity expected of salmon calcitonin, based on its known and well-characterized mechanism of action, and (2) has the same activity as the salmon calcitonin in the listed drug, Miacalcin NS.

It is well recognized that the inhibition of bone resorption in the setting of continued bone formation will lead to increases in bone density. In addition, it is well established in the published literature that salmon calcitonin, mediated through the calcitonin receptor on osteoclasts, inhibits bone resorption and thereby increases bone mineral density.[5] Based on the literature, we believe that the pharmacodynamic effect of any salmon calcitonin drug product on reducing serum beta-CTx (C-telopeptides of Type 1 collagen, corrected for creatinine)—a widely accepted marker of bone resorption—is an adequate surrogate

[5] See, e.g., Reginster, J.Y., Effect of Calcitonin on Bone Mass and Fracture Rates, *Am J Med* 1991, 91:19s-22s; Cranney, A., P. Tugwell, N. Zytaruk et al., Meta-Analyses of Therapies for Postmenopausal Osteoporosis, VI. Meta-Analysis of Calcitonin for the Treatment of Postmenopausal Osteoporosis, *Endoc Rev* 2002, 23:540-551.

for the increase in bone mineral density expected by the known mechanism of action of calcitonin. Therefore, it was appropriate for Unigene to establish that Fortical has the same active ingredient as Miacalcin NS by providing data in the 505(b)(2) application demonstrating that the pharmacodynamic effects of Fortical on bone resorption (as assessed by changes in serum beta-CTx) are comparable to those of Miacalcin NS.

Evidence of Fortical's pharmacodynamic equivalence to Miacalcin was shown in a double-blind, active-controlled, 24-week study of 134 postmenopausal women, randomized in a one-to-one ratio to either Fortical 200 IU per day or Miacalcin 200 IU per day. The primary efficacy outcome was the change in serum levels of beta-CTx from baseline to Week 12. The groups were well matched for baseline characteristics, with participants having a mean age of 66 years and average lumbar spine bone mineral density of 0.800 gram (gm)/centimeter $(cm)^2$ (approximate T-score of -2.53). In the primary analysis of efficacy, the difference between treatment groups in the mean change from baseline to Week 12 in beta-CTx was –0.08 to 0.06 nanogram (ng)/milliliter (mL), well within the prespecified equivalence margin of ± 0.20 ng/mL. These results indicate that the pharmacodynamic effects of Fortical on bone are noninferior to those of Miacalcin NS (i.e., the observed differences between Fortical and Miacalcin NS are not clinically meaningful based on markers of bone resorption).[6]

You state that FDA has repeatedly recognized that two recombinant products may have different safety and efficacy profiles, and you state that such differences may be found between a recombinant product and a synthetic product. You maintain that this is especially important because the manner in which calcitonin works in osteoporosis is unknown, referring to a statement in the Miacalcin NS package insert that describes the bone-related actions of calcitonin as "'not completely elucidated'" (Petition at 9, quoting Miacalcin NS package insert at 2). You state that, because the recombinant product requires enzymatic alpha amidation for full activity, even small amounts of non-amidated peptide could not fit the same receptors as the synthetic product, or the recombinant product might fit different receptors or more receptors, and these differences might affect efficacy, safety, or both. Therefore, you conclude that a recombinant calcitonin and a synthetic calcitonin can be shown to have the same effectiveness only by demonstrating through an appropriate clinical trial that recombinant calcitonin does what calcitonin is supposed to do (i.e., have a therapeutic effect on the fracture rate). You further state that any safety issues must be resolved though appropriate animal and human studies (Petition at 9).

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[6] You state that although the bone mineral density studies conducted on Miacalcin NS were 2-year studies, the Fortical study was only a 6-month study. Therefore, you claim that FDA cannot know whether Fortical would even be comparable to Miacalcin NS with respect to bone mineral density at 2 years (Petition at 8). We disagree. Given the sameness of the primary, secondary, and tertiary chemical structures of the salmon calcitonin in Miacalcin NS and Fortical, there is no scientific basis to believe that these drugs would not have a similar pharmacodynamic effect and that this similarity would not persist over time. Moreover, the results of the Fortical study confirm that Fortical has a pharmacodynamic effect similar to that of Miacalcin NS.

We disagree for several reasons. First, we have a much greater understanding of the mechanism of action of calcitonin on bone than we did at the time of the approval of the Miacalcin NS package insert to which you refer. We know that calcitonin acts on bone by binding to and signaling through the calcitonin receptor. In addition, both Fortical and Miacalcin NS contain alpha-amidated calcitonin as the active drug substance. Based on criteria used to assess biological activity and other quality attributes, these drug substances are indistinguishable. As stated above, Unigene provided evidence demonstrating that Fortical is not inferior to Miacalcin NS in effect on bone resorption, which is evidence of appropriate receptor activity. In addition, we have no reason to believe that any differences in the biochemical processing of Fortical relative to Miacalcin NS would somehow preferentially affect fracture efficacy without influencing bone resorption and formation, as measured by biochemical markers of bone turnover and bone mineral density.

Moreover, as stated in section II.A of this response, we approved Miacalcin NS based on data regarding its effects on bone mineral density, not on fracture data. To obtain approval of Fortical for the same indication as Miacalcin NS, Unigene was required to, among other things, provide clinical evidence demonstrating that Fortical has the same active ingredient as Miacalcin NS, so that the Fortical 505(b)(2) application could rely on the effectiveness finding for Miacalcin NS. Unigene met this requirement by demonstrating in a 24-week clinical study that Fortical had noninferior pharmacodynamic effects on bone resorption. The pharmacodynamic study also provided evidence that the overall safety of Fortical is indistinguishable from that of Miacalcin NS. Therefore, beyond the pharmacodynamic study and other studies described in section II.B.2 of this response (in addition to the data in the Miacalcin NS NDA on which Unigene relies), no additional animal or human studies were required to demonstrate Fortical's safety or effectiveness acting through the calcitonin receptor.

2. Other Evidence Supporting Approval

In addition to establishing the sameness of Fortical's active ingredient through a pharmacodynamic comparison to Miacalcin NS, Unigene established that Fortical and Miacalcin NS have a comparable BA/BE profile. In the bioequivalence study submitted as part of the 505(b)(2) application for Fortical, Unigene compared the relative bioavailability of Fortical to that of Miacalcin NS in a multidose, crossover study of 47 healthy female volunteers. On each day of dosing, subjects received a total of 2400 IU of Fortical or Miacalcin NS over a 100-minute period. The C_{max} and AUC values for Fortical were 56 pg/mL and 891 pg.min/mL compared to 47 pg/mL and 716 pg.min/mL for Miacalcin NS. Because the upper bounds of the 90 percent confidence intervals for the ratios of the Fortical pharmacokinetic parameters to those of Miacalcin NS were above the 125 percent acceptance interval (the standard upper bound for bioequivalence), Fortical is not, by regulatory standards, bioequivalent to Miacalcin NS. However, because Fortical was slightly more, rather than less, bioavailable than Miacalcin NS, and the activity of these drugs on bone (in the 24-week clinical study) was shown to be indistinguishable, this lack of bioequivalence is not deemed clinically significant.

From a safety perspective, the increased bioavailability of Fortical did not demonstrate any new or increased safety signals. In the small Phase 1 studies using high-dose salmon calcitonin (2000 IU, ten times the prescribed dose), nasal symptoms and dizziness were more commonly experienced with Fortical than Miacalcin NS. However, in the larger, 24-week pharmacodynamic study using the prescribed 200 IU dose, symptoms of nausea, dizziness, and postural hypotension were not seen, and nasal symptoms were equally distributed between the Fortical and Miacalcin NS treatment groups. In addition, there were no clinically significant laboratory or ECG changes noted in any of the trials.

The Fortical 505(b)(2) application also included pharmacology, pharmacokinetic, and toxicology studies in animals. The main purpose of the pharmacology studies was to demonstrate the equivalence of the recombinant peptide (Fortical) to the synthetic peptide (Miacalcin NS). The pharmacokinetic studies were carried out to characterize the pharmacokinetic profile of Fortical by different administration routes and to compare it with Miacalcin NS. The aim of the toxicology studies was to assess the toxicity profile of Fortical and to compare the toxicity of Fortical to that of Miacalcin NS. Information on the carcinogenic potential and reproductive toxicity of salmon calcitonin was previously obtained in studies with synthetic salmon calcitonin, so there was no need for additional clinical studies. The 28-day rat intranasal toxicity study was the principal nonclinical toxicology requirement. This study showed that there was a slight increase in the incidence of focal rhinitis in males, as compared to the saline control and Miacalcin NS, at 30- to 15-fold human exposure. This effect may have been due to the Fortical excipients. As stated above, studies in humans showed that nasal symptoms (including rhinitis) occurred equally with Fortical and Miacalcin NS.

You state that synthetic salmon calcitonin is known to be immunogenic and that there is some thought that the immunogenicity affects the efficacy of the drug. You state that it seems likely that a recombinant calcitonin product will have a pattern of immunogenicity different from that of the synthetic product, and might therefore differ in safety as well as efficacy. Therefore, you claim that immunogenicity differences could significantly alter the risk-benefit profile of recombinant calcitonin versus synthetic calcitonin, making animal and human data on Fortical itself (rather than unsupported assumptions about its similarity to Miacalcin NS) essential to approval (Petition at 9).

Using archived samples from the 24-week pharmacodynamic study, Unigene examined the comparative immunogenicity of Fortical and Miacalcin NS. The data showed that the two drugs have essentially the same immunogenicity (there was no difference in binding or neutralizing antibody formulation). Therefore, the immunogenicity of Fortical compared to that of Miacalcin NS provides no basis for concluding that Fortical is not as safe as Miacalcin NS and thus no basis for requiring additional clinical studies of Fortical.

C. Request for Advisory Committee Meeting

In your April 27, 2005, response to Unigene's comments, you state that there are many unresolved scientific issues concerning the Fortical NDA and request that we refer these

issues to an advisory committee so that we can obtain the committee's recommendations. As explained above, we resolved all relevant scientific issues concerning the Fortical NDA, concluding that Unigene had provided sufficient information necessary for the approval of Fortical. Therefore, we determined, in our discretion under 21 CFR 14.172, that there was no need to refer any issues to an advisory committee prior to taking action regarding the Fortical NDA.

III. CONCLUSION

In accordance with section 505(b)(2) of the Act and our policy on 505(b)(2) applications, Unigene submitted evidence demonstrating that its recombinant salmon calcitonin product, Fortical, has the same active ingredient as Miacalcin NS and that it is appropriate for the Fortical NDA to rely on FDA's findings concerning the safety and effectiveness of Miacalcin NS. For the reasons stated in this response, clinical data regarding a therapeutic effect on fracture rate were not required for the approval of Fortical. Therefore, your petition is denied.

Sincerely,

Steven K. Galson, M.D., M.P.H.
Acting Director
Center for Drug Evaluation and Research