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Food and Drug Administration  
Department of Health and Human Services  
Room 1061  
5630 Fishers Lane  
Rockville, Maryland 20852

Re: Comments to Citizen Petition, Docket No. 2004P-0015

Unigene Laboratories, Inc. (“Unigene”) submits these comments in response to the January 9, 2004 Citizen Petition filed by Buc & Beardsley requesting that the Food and Drug Administration (“FDA”) deny approval of any New Drug Application (“NDA”) for recombinant salmon calcitonin (“rsCT”) nasal spray for the prevention or treatment of osteoporosis that lacks clinical data demonstrating the efficacy of the specific rsCT product in preventing or treating bone fractures.<sup>1</sup> The Citizen Petition focuses on Miacalcin<sup>®</sup> Nasal Spray (“Miacalcin”), an approved synthetic salmon calcitonin (“ssCT”) nasal spray, and Fortical<sup>®</sup> Nasal Spray, an rsCT nasal spray product that was submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (“FDC Act”) by Unigene. With these comments, Unigene responds to the issues raised by the Citizen

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<sup>1</sup> See Buc & Beardsley Citizen Petition, Docket No. 2004P-0015 (Jan. 9, 2004) (“Citizen Petition”).



Petition and shows them to be without merit. In addition, some issues raised in the Citizen Petition relate, in part, to specifics about Unigene's product and the data in its NDA. The data and other information contained in the Fortical NDA are confidential. In order to preserve the confidentiality of such data and information, in this response to the Citizen Petition, Unigene references its NDA, but does not provide specific data.

As we show below, nothing in the FDC Act, FDA regulations, or FDA's policy pertaining to 505(b)(2) applications requires the type of efficacy data advocated by the Citizen Petition for FDA to approve Unigene's application. Moreover, the Fortical NDA meets all requirements for approval. Therefore, the relief requested by the Citizen Petition should be denied, and the Fortical NDA must be approved.

## I. Response to Specific Arguments in the Citizen Petition

### A. The Efficacy Data Advocated by the Citizen Petition Are Not Required

Section 505(b)(2) of the FDC Act permits submission of an NDA for which the safety and effectiveness investigations "relied upon by the applicant for 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."<sup>2</sup> The type of information that an applicant can rely on includes FDA's finding of safety and effectiveness for an approved drug.<sup>3</sup> FDA's regulations state that an

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<sup>2</sup> 21 U.S.C. § 355(b)(2).

<sup>3</sup> FDA, Draft Guidance for Industry, Applications Covered by Section 505(b)(2), at 2-3 (Oct. 1999) ("505(b)(2) Guidance").



applicant may submit a 505(b)(2) application for “a drug product that represents a modification of a listed drug . . . and for which investigations other than bioavailability or bioequivalence studies are essential to the approval of the changes. . . . This application need contain only that information needed to support the modification(s) of the listed drug.”<sup>4</sup> FDA’s 505(b)(2) Guidance also makes it clear that when an applicant seeks approval of a product that includes a change from a previously approved drug product, “an application may rely on the Agency’s finding of safety and effectiveness of the previously approved product, coupled with the information needed to support the change from the approved product.”<sup>5</sup>

FDA recently stated that its

longstanding 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. . . . The 505(b)(2) pathway permits sponsors and FDA to determine what studies are necessary to support the approval of the new aspect of the drug. It then allows sponsors to target drug development resources to studies needed to support the proposed difference or innovation.<sup>6</sup>

Therefore, while it is true as the Citizen Petition asserts that the standards for approval are not relaxed for a 505(b)(2) application, it is also true that the relevant additional data to be submitted by the applicant are the data necessary to support the modification. The

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<sup>4</sup> 21 C.F.R. § 314.54(a).

<sup>5</sup> 505(b)(2) Guidance at 3.

<sup>6</sup> Letter from Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research, to Katherine M. Sanzo, Esq., et al., at 3-4 (Oct. 14, 2003) (“Woodcock Letter”).



505(b)(2) application process does not require the applicant to reestablish what was determined by the original NDA approval.<sup>7</sup>

The Citizen Petition states that “[a] 505(b)(2) applicant can rely to some degree on what FDA has previously decided with respect to another drug, but it has the burden of showing that it is scientifically permissible to reach the same conclusions for its drug as FDA previously reached for the first drug.”<sup>8</sup> In fact Unigene did meet this burden; the extensive physico-chemical, pre-clinical, and clinical comparisons Unigene conducted (described briefly below and in detail in the Fortical NDA) all establish conclusively that it is scientifically permissible for FDA to draw the same conclusion for Fortical as FDA did for Miacalcin. Furthermore, according to FDA, “[t]he nature and extent of the reliance on the agency’s conclusion of safety and effectiveness for a listed drug are the same for applications under section 505(b)(2) and 505(j); it is only the amount of additional data necessary to support the approval of the proposed drug product that may differ.”<sup>9</sup> Submission of a 505(b)(2) application for a calcitonin nasal spray should not open the door for a requirement for additional data to support the original approval. Nor

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<sup>7</sup> FDA has, in fact, suggested that additional review of the data in the original NDA is inappropriate. While FDA’s approval of a 505(b)(2) application indirectly relies on the data in the original NDA, FDA is actually relying on its prior conclusions regarding the safety and effectiveness of the drug product. Id. at 10, n.14.

<sup>8</sup> Citizen Petition, at 7.

<sup>9</sup> Woodcock Letter, at 15. FDA’s 505(b)(2) Guidance states essentially the same thing – FDA’s regulation pertaining to 505(b)(2) applications “permits a 505(b)(2) applicant to rely on the Agency’s finding of safety and effectiveness for an approved drug to the extent such reliance would be permitted under the generic drug approval provisions at section 505(j).” 505(b)(2) Guidance, at 3.



does it open the door for reevaluation of the Miacalcin data. As FDA has repeatedly stated, the only data required in a 505(b)(2) application are data to support the modification or change from the original product.

This is particularly true if the change does not represent any change in indication. Miacalcin “is indicated for the treatment of postmenopausal osteoporosis in females greater than 5 years postmenopause with low bone mass relative to healthy premenopausal females.”<sup>10</sup> Fortical will have the same indication as Miacalcin does, and the package insert and labeling will be nearly identical to that of Miacalcin. The Miacalcin package insert states that the efficacy evidence for the product “is based on increases in spinal bone mineral density observed in clinical trials.”<sup>11</sup> The package insert makes no mention of fracture data or a demonstrated effect on fractures. The same is true for Fortical. If a 505(b)(2) product will make the same claims as Miacalcin (including making no reference to fracture rates), which is the case for Fortical, it is not appropriate to require additional data from a 505(b)(2) applicant related to the already-approved indication.

Given that a 505(b)(2) application for a salmon calcitonin nasal spray that relies on FDA’s approval of Miacalcin would only require additional data to support the modification to the product, the Citizen Petition incorrectly asserts that a 505(b)(2) application with the active ingredient of rsCT requires fracture data of the same amount

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<sup>10</sup> Novartis, Miacalcin® Nasal Spray Package Insert, at 3 (Apr. 2003) (“Miacalcin PI”).

<sup>11</sup> Id.



or greater than FDA required for Miacalcin and bone mineral density data (“BMD”) of the same duration as that provided for Miacalcin.

The type of data required in the 505(b)(2) application depends on how the 505(b)(2) product differs from the approved product. Modifications that are acceptable for 505(b)(2) applications run the gamut and include a change to a recombinant active ingredient.<sup>12</sup> In this instance, the modification that requires additional data is the use of recombinant as opposed to synthetic salmon calcitonin. The data to bridge an rsCT nasal spray and an ssCT nasal spray would not be the fracture data advocated by the Citizen Petition. Rather, the comparability data provided in the Fortical NDA are more than sufficient to support the modification from ssCT to rsCT. Moreover, the Citizen Petition’s assertion that the study to support the modification must be of the same duration as the original study is unfounded. There is no requirement that such a bridging study be two years in duration. The scope of the additional data necessary for approval of a 505(b)(2) application for rsCT nasal spray is limited to that which is necessary to support the change – there is nothing that suggests that a two-year study of BMD is

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<sup>12</sup> 505(b)(2) Guidance, at 4-6 (stating that “applications that may be accepted pursuant to section 505(b)(2)” include “Naturally derived or recombinant active ingredient. An application for a drug product containing an active ingredient(s) derived from animal or botanical sources or recombinant technology where clinical investigations are necessary to show that the active ingredient is the same as an active ingredient in a listed drug.”). In fact, GlucaGen is just one example of an approval of an NDA in which the initial approval was for a naturally derived (extracted) product and the 505(b)(2) NDA product was made, as here, by a recombinant technology. Letter from Solomon Sobel, M.D., Director, Division of Metabolic and Endocrine Drug Products, ODE II, CDER, to Barry Reit, Ph.D, Novo Nordisk Pharmaceuticals, Inc. (NDA 20-918), available at [http://www.fda.gov/cder/foi/appletter/1998/20918\\_ltr.pdf](http://www.fda.gov/cder/foi/appletter/1998/20918_ltr.pdf) (June 22, 1998).



required to demonstrate the safety and effectiveness of this modification or any other modification to Miacalcin.

B. The Citizen Petition Incorrectly Describes the Data in the Fortical NDA

The Citizen Petition incorrectly states that the Fortical NDA contains only a single study on Fortical itself.<sup>13</sup> In fact, multiple clinical studies (pharmacokinetic (“PK”) and pharmacodynamic (“PD”)) were performed, all in comparison to Miacalcin. These studies are in Unigene’s NDA and are confidential.

The Citizen Petition’s assertion that the finding of comparability of Fortical to Miacalcin is itself suspect is unfounded.<sup>14</sup> The Fortical clinical program was implemented after multiple discussions with FDA and confirmation from FDA that the program was appropriate and information in the Fortical NDA demonstrate the validity of Unigene’s program to establish comparability.

C. The Citizen Petition Misinterprets the Data Regarding Calcitonin Compared to Calcium and Vitamin D

The Citizen Petition incorrectly claims that the increase in BMD reported for Fortical is less than that reported for calcium and vitamin D treatment alone.<sup>15</sup> Review of the article referenced by the Citizen Petition demonstrates that the results have been misinterpreted. First, the 2.12% increase in BMD at the spine reported for calcium and

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<sup>13</sup> Citizen Petition, at 7.

<sup>14</sup> Id. at 8, n 31.

<sup>15</sup> Id. at 2.



vitamin D occurred at 3 years (the Fortical data were at 6 months).<sup>16</sup> Second, the placebo in the cited study also increased by 1.22%.<sup>17</sup> Third, the results cited include those for both men and women. A closer inspection of the data reveals that the comparison for women (the test group in the Fortical clinical studies) demonstrated that spine BMD increased from 0.78 in placebo to 1.41 in the calcium and vitamin D treated group with a p value of 0.32 (NS).<sup>18</sup>

Moreover, the results from the Fortical study clearly show a more robust and significant response at both spine and hip after only 6 months of treatment. These results are in agreement with those reported in the package insert for Miacalcin, which states that a significant increase in spine BMD was realized as early as 6 months.<sup>19</sup> In addition there was no difference in the BMD response between Fortical and Miacalcin. Finally, publications from experts in the field have established that calcium and vitamin D supplementation potentiates the effectiveness of estrogen and calcitonin-based antiresorptive therapies for osteoporosis (a copy of a review article is attached as Appendix A).

D. The Citizen Petition Incorrectly States that Surrogate Markers Are Not Appropriate

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<sup>16</sup> B. Dawson-Hughes et al., Effect of Calcium and Vitamin D Supplementation on Bone Density in Men and Women, 65 Years of Age or Older, 337 N. Eng. J. Med. 670, 672 (1997).

<sup>17</sup> Id.

<sup>18</sup> Id.

<sup>19</sup> Miacalcin PI, at 4.



The Citizen Petition states that it is not sufficient to establish that the drug affects some factor that is not necessarily correlated with therapeutic benefit.<sup>20</sup> However, Unigene performed a comparative clinical study with Miacalcin that demonstrated comparable pharmacologic response. The bone turnover markers utilized were those that are approved by FDA for monitoring bone resorption. The same surrogate markers have been measured in all currently approved antiresorptive therapies (SERMS and bisphosphonates). The results obtained for Fortical and Miacalcin are consistent with those reported in the literature for other antiresorptive drugs. Furthermore, the selection of the surrogate markers was made in concurrence with the Agency.

E. Clinical Studies Demonstrate that the Safety Profiles of Fortical and Miacalcin Are Similar

The Citizen Petition claims that Fortical might contain non-amidated calcitonin, which may differ in its receptor binding characteristics compared to Miacalcin.<sup>21</sup> Unigene has presented in its NDA extensive data, including chromatographic evidence and validation data, that demonstrate that non-amidated rsCT is removed during the purification of the API. Additionally, no significant amounts of glycine-extended peptide could be demonstrated in the final product by any of the appropriate analytical procedures employed.

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<sup>20</sup> Citizen Petition, at 3.

<sup>21</sup> Id. at 9.



The Citizen Petition also raises the issue of the potential immunogenicity of calcitonin.<sup>22</sup> Unigene acknowledges the importance of this issue and conducted a thorough comparative study measuring the immunogenicity of Fortical and Miacalcin following six months of daily dosing. The results, which were provided to FDA in the Fortical NDA, demonstrated that the total immune response and the response of neutralizing antibodies were the same for both drugs.

## II. Fortical Meets All Requirements for Approval

Recognizing the importance of determining whether Fortical and Miacalcin are comparable, Unigene worked with FDA to develop a comprehensive comparability strategy. Unigene performed tests in each of the categories identified by FDA in its Guidance Concerning Demonstration of Comparability,<sup>23</sup> even though Unigene did not necessarily have to perform all of the tests in order to demonstrate comparability. In addition, Unigene received FDA's concurrence in meetings and other discussions that, in fact, Unigene had demonstrated that rsCT and ssCT are physico-chemically and structurally identical. Furthermore, FDA has repeatedly found Unigene's approach of submitting a 505(b)(2) NDA and the clinical program (as an additional "bridge" to the previous FDA findings with respect to the Miacalcin product) to be appropriate.

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<sup>22</sup> Id.

<sup>23</sup> FDA, Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-Derived Products (Apr. 1996).



Salmon calcitonin is a 32 amino acid, non-glycosylated peptide hormone. The simple structure of this molecule (limited secondary structure (a single disulfide bond) and no tertiary structure) lends itself to rigorous physico-chemical analysis yielding unambiguous results. Unigene performed an extensive series of comparative analytical studies to establish that rsCT and ssCT are identical. The analysis compared rsCT with International Reference Standards for ssCT and Miacalcin. The analytical results demonstrated unequivocally that salmon calcitonin manufactured by chemical synthesis is indistinguishable from salmon calcitonin manufactured by recombinant DNA technology. These data were all submitted to FDA in the Fortical NDA.

In addition to the physico-chemical analysis, comparative pre-clinical PK and PD studies were performed. These studies demonstrated that the PK characteristics of the molecules as well as the PD response were comparable.

Unigene also performed clinical PK and PD studies. The bioavailability of Fortical and Miacalcin were shown to be comparable. The PD study demonstrated that the biological activities of Fortical and Miacalcin are equivalent.

Moreover, the clinical studies demonstrated no statistically significant differences between the safety profiles of Fortical and Miacalcin. As mentioned above, a thorough immunogenicity study was carried out that characterized the antibody response to Fortical and Miacalcin following 6 months of daily dosing in osteoporotic women. The results of this study showed that there was no significant difference in total number of patients with circulating anti-sCT antibodies and the subset that demonstrated neutralizing activity, which further attests to the comparability of the molecules.



The level and extent of comparison performed for this well-characterized peptide meet or exceed what is expected in a comparability protocol. The data clearly establish that salmon calcitonin manufactured by chemical synthesis is physico-chemically indistinguishable from salmon calcitonin manufactured by recombinant technology, Fortical and Miacalcin are comparable formulations, and there is no statistically significant difference between the two products in terms of clinical performance. It is therefore scientifically valid for FDA to reach the same conclusions regarding the safety and efficacy of Fortical as it did for Miacalcin.

### III. Conclusion

Contrary to the positions asserted in the Citizen Petition, a 505(b)(2) application for rsCT nasal spray is not required to establish safety and effectiveness through bone fracture data or provide BMD data for the same duration as that in the approved NDA. Moreover, Unigene has demonstrated in its confidential NDA that Fortical fulfills the requirements for approval of the 505(b)(2) application. Therefore, the Citizen Petition should be denied and Unigene's NDA must be approved.

Sincerely,

Ronald S. Levy, Ph.D  
Executive Vice President