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April 27, 2005

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

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

In its January 9, 2004 Citizen Petition, Buc & Beardsley asked FDA to deny approval of any New Drug Application for recombinant salmon calcitonin (rsCT) nasal spray, such as Unigene Laboratories, Inc.'s Fortical, for prevention or treatment of osteoporosis that contains as "proof" of efficacy only bone mineral density data or other markers of bone cell activity but lacks clinical data demonstrating the efficacy of the specific rsCT product for which approval is sought in preventing or treating bone fractures.

Unigene's comments, filed on April 11, 2005, claim to respond fully to the arguments in the Citizen Petition, but in fact do not do so. Instead, although the Unigene comments provide several generalizations about Section 505(b)(2) approvals, they do not address at all, or do not address directly, several key reasons why the Unigene NDA does not meet the legal and scientific standards for approval. Because there are so many unresolved scientific issues about this NDA, Buc & Beardsley requests an advisory committee meeting prior to approval to review these issues and provide advice to FDA with respect to them.

Unigene's response does acknowledge that its NDA does not contain fracture data., but argues that fracture data should not be required. Instead, it says, it should be enough to "bridge" the differences between rsCT and the approved Miacalcin synthetic salmon calcitonin product by various pharmacokinetic, pharmacodynamic, and other assessments which purportedly demonstrate that the two products are "comparable." Both the assertion that fracture data ought not be required and Unigene's assertion that "bridging" to show comparability ought to be sufficient are incorrect.

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Unigene rests its argument that fracture data ought not be required in large part on the assertion that fracture data were not required for the Miacalcin approval and should not, therefore, be required for Fortical. But FDA did require fracture data before it would approve the Miacalcin nasal spray calcitonin, and the reasons why it did so apply not only to Miacalcin but also with special force to Fortical.

As outlined in the Citizen Petition, FDA and its osteoporosis advisory committee have been concerned for many years with a problem presented by non-estrogenic agents for preventing and treating osteoporosis: positive changes in bone mineral density do not necessarily correlate with improvements in fracture rates, and may actually be inversely correlated with fracture rates, as was the case with fluoride, or have no effect on fracture rates, as was the case with etidronate. In light of this issue, FDA's advisory committee voted unanimously in favor of the agency's requiring fracture data before approving an additional, prevention indication for the injectable form of synthetic calcitonin. Those data – the first two years of the PROOF study, showing favorable trends in fracture rates – were before the advisory committee that recommended approval of the nasal spray calcitonin product, and were before FDA when it approved the product.

As it turned out, however, the final results of PROOF were equivocal at best. Only the 200 IU dose of calcitonin nasal spray reduced the risk of fractures, but neither the 100 IU nor the 400 IU dose did so, and there was no consistent relationship between calcitonin (or other biochemical markers) and the risk of fractures. Four members of the Division of Metabolic and Endocrine Drug Products (Dr. Eric Colman, Mr. Randy Hedin, Ms. Joslyn Swann, and Dr. David Orloff) commented on these data as follows:

[T]he fact that the bone mineral density data and fracture risk trends did not correlate in this 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.¹

It is precisely because there is not a correlation between BMD and fracture for synthetic calcitonin that it is not enough that a different, recombinant calcitonin product show "comparability" on BMD and other biochemical markers. The Miacalcin approval needed fracture data, limited though they were, for that very reason. When A (BMD) is not correlated with B (fracture data), neither Unigene nor any other sponsor of an NDA for a non-estrogenic product can rest on the assumption that if C is "comparable" to A, it will correlate with B. FDA should not approve still another product whose effect on fractures is not just unclear but unstudied.

1. E. Colman et al., A brief history of calcitonin, 359 The Lancet 885 (March 9, 2002).

Nor is it clear that Unigene has even demonstrated comparability. For one thing, although the Miacalcin NDA had two-year studies of BMD, Unigene admits it has only 6 month studies. Six months is not even close to comparable to two years. At a minimum, FDA must require BMD studies of sufficient duration to firmly establish an effect on that parameter.

The “comparability” of Fortical to Miacalcin is also suspect on other grounds. In its response, Unigene repeatedly asserts that Fortical and Miacalcin are not different or are not statistically significantly different with respect to parameters such as BMD, amounts of glycine-extended peptide, immunogenicity, bioavailability, and clinical performance. But “not being different” and “not being statistically significantly different” definitely do not mean “the same,” and do not necessarily mean close enough to be “comparable.” From Unigene’s description of its studies, none (including the ASBMR-reported study on which the NDA surely rests to a substantial degree) is of a non-inferiority design. Accordingly, whether they are adequate to rule out meaningful differences is uncertain at best. Especially in this situation, where the kind and extent of difference that could be meaningful is unknown, a very high degree of comparability, verging on sameness, is essential. If Unigene’s studies were incapable of demonstrating such a high degree of comparability, verging on sameness, as seems likely, then they are insufficient for approval.

In its response, Unigene also argues that calcium and vitamin D supplementation potentiates the effectiveness of calcitonin-based antiresorptive therapies for osteoporosis. That calcium and vitamin D supplementation are well known to be useful, indeed necessary, in osteoporosis prevention and treatment is now axiomatic. But what is the relevance of that observation to comparisons of recombinant salmon calcitonin to synthetic salmon calcitonin? The article which Unigene provided as Appendix A does not demonstrate that (or even discuss whether) the same amounts of calcium and vitamin D are necessary to potentiate recombinant and synthetic salmon calcitonin, respectively. The article does, however, raise the question of whether a 200 IU dose of calcitonin is sub-optimal. Even though that is the dose of Miacalcin FDA approved, the article is hardly a resounding endorsement of further approvals of that dose, especially of a different drug.

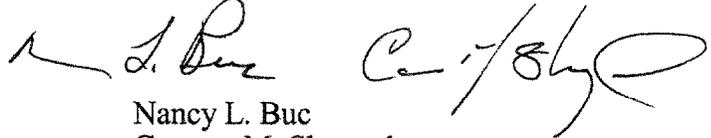
Finally, although the ICH E1a Guidelines suggest that 300-600 subjects be studied for safety for at least six months, it does not appear that the Fortical, which is for all practical purposes a new chemical entity, has been studied in that manner. If not, safety remains an important unresolved issue.

Buc & Beardsley reiterates its request that FDA not approve any NDAs for rsCT nasal spray, such as Unigene’s Fortical, unless that NDA contains solid clinical proof of efficacy for

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preventing or treating bone fractures. We also ask that the scientific issues raised by our Citizen Petition, Unigene's response, and these additional comments, be referred to an advisory committee so that FDA can obtain the committee's recommendations.

Sincerely,

Handwritten signatures of Nancy L. Buc and Carmen M. Shepard.

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