DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-772/S-005

QOL Medical
c/o Certus International
Attention: Robert Wolfangel, Ph.D., Senior Director of Regulatory Affairs
1422 Elbridge Payne Road, Suite 200
St. Louis, MO 63017

Dear Dr. Wolfangel:

Please refer to your supplemental new drug application dated August 15, 2008, received August 19, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Sucraid (sacrosidase) Oral Solution, 8,500 IU/mL.

We acknowledge receipt of your submissions dated August 27, September 3, 9, 11 and 30, October 8, 9 and 27, and November 6 and 18, 2008. This supplemental new drug application provides for changes in the manufacture of Sucraid (sacrosidase) Oral Solution.

We also refer to a teleconference held on October 24, 2008 in which FDA informed you that you could release newly manufactured product lots to patients in advance of FDA taking a final action on this application.

We completed our review of this supplemental new drug application, as amended. This supplement is approved, for use as recommended in the agreed-upon labeling text, submitted on November 18, 2008.

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amended the FDCA to authorize FDA to require sponsors of approved drugs to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)). FDA may also require a sponsor of an approved drug to develop and comply with a Risk Evaluation and Mitigation Strategy (REMS) (section 505-1 of the FDCA) if FDA determines that a REMS is necessary to ensure that the benefits of the drug outweigh the risks. These provisions took effect on March 25, 2008.

The approved labeling for Sucraid discusses the potential for serious allergic reactions in some patients based on an observation of an adverse event in a single patient during the clinical trials on the product. Since Sucraid was approved in April 1998, changes in manufacturing for this product have been made which may lead to more frequent serious allergic reactions. Analysis of the newly manufactured Sucraid product indicates that some amount of papain is likely to be present in the drug substance. Papain is known to cause allergic reactions in some people. We consider this information to be “new safety information” as defined in FDAAA.

POSTMARKETING REQUIREMENTS UNDER 505(o)

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the known risk of serious allergic reactions associated with the use of Sucraid.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is therefore not sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required, pursuant to section 505(o)(3) of the FDCA, to conduct the following study:

1. Conduct a one-year observational study in pediatric and adult patients using the newly manufactured Sucraid to evaluate the incidence of serious adverse reactions, including anaphylaxis and serious allergic reactions.

   You have previously agreed on November 17, 2008, to conduct this study according to the following timetable:

Protocol submission:	December 2008
Study Start Date:	February 2009
Final Report Submission:	February 2012

Submit the protocol to your IND 53-372, with a cross-reference letter to this NDA 20-772. Submit all final report(s) to your NDA 20-772. Use the following designators to prominently label all submissions, including supplements, relating to this postmarketing study as appropriate:

Required Postmarketing Protocol under 505(o)
Required Postmarketing Final Report under 505(o)
Required Postmarketing Correspondence under 505(o)

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for Sucraid to ensure that the benefits of the drug outweigh the risks. The REMS consists of a communication plan, elements to assure safe use, an implementation system, and a timetable for assessments of the REMS. We have determined that the REMS must include elements to assure safe use to mitigate the risk of serious allergic reactions by assuring that prescribers are knowledgeable about the risks of Sucraid. Your proposed REMS, appended to this letter, submitted on November 18, 2008, is approved. Information needed for assessment of the REMS should include but not be limited to:

a. An assessment of prescriber compliance with elements of certification: completing the prescriber survey regarding their patients' experience using the new product.
b. An assessment of caregivers' and/or patients' experience using the new product.
c. Report on failures to adhere to distribution of the caregiver and patient letters and surveys with each shipment of Sucraid.

POSTMARKETING COMMITMENTS NOT REPORTABLE UNDER FDCA § 506B[1]

As documented in your letter dated, October 9, 2008, received October 14, 2008, you agreed to the following postmarketing commitments:

2. To revise drug substance release specifications to include a quantitative release assay for papain content. The new specification will be submitted by August 31, 2009.

3. To complete and submit the results of an enzyme kinetic study (determination of K_m and K_{cat}) comparing the sacrosidase drug substance produced by **(b) (4)** with the drug substance produced by **(b) (4)** The final report will be submitted in January 2009.

4. To evaluate the use of K_m and K_{cat} determinations in the drug substance and drug product release and stability specifications. Results of this evaluation will be submitted by March 31, 2009.

5. To revise the drug substance release and stability specifications to include a specification for specific activity utilizing an upper and lower limit. The new specification will be submitted by August 31, 2009.

6. To revise the drug substance release and stability specifications to include SDS-PAGE analyses with quantitative measures of mobility of various bands and protein content. The new specifications will be submitted by October 31, 2009.

7. To provide the results of the anion exchange HPLC analyses comparing sacrosidase lots manufactured by **(b) (4)** with sacrosidase lots manufactured by **(b) (4)**. The final study report will be submitted by November 30, 2009.

[1] These chemistry, manufacturing and control commitments are not reportable under FDCA section 506B or 21 CFR 314.81(b)(vii) which only require reporting of clinical safety and efficacy and non-clinical toxicology commitments.

8. To investigate the use of orthogonal methods to assess product purity in addition to the SDS-PAGE analysis. The results of this investigation will be submitted by October 31, 2009.

9. To develop and institute a plan for sacrosidase purification operations consistent with drug GMPs, which will be operative within the food GMP plant, by providing the following:

    a. A detailed plan for implementation of a quality systems approach to upgrade the manufacturing of sacrosidase drug substance to pharmaceutical GMP standards by April 30, 2009;

    b. A progress report after three lots of drug substance have been manufactured according to GMPs; the timeline for submission of this report will be described in the implementation plan.

Submit chemistry, manufacturing, and controls protocols and all study final reports to your NDA 20-772.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Matthew Scherer, Regulatory Project Manager, at (301)796-2307.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Director
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Donna Griebel

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