



Memorandum

Date: July 29, 2004

From: Division of Petition Review (HFS-265)
Chemistry Review Team

Subject: FAP 4A4754; Hyman, Phelps and McNamara, P.C., on behalf of zuChem, Inc., Submissions of 6/17/2004 and 7/19/2004. Mannitol produced by fermentation using the microorganism *Lactobacillus intermedius* (*fermentum*).

To: Division of Petition Review (HFS-265)
Regulatory Group II
Attention :C. Johnston

ReF

In the chemistry memorandum dated 4/20/04 regarding the subject petition, we noted two chemistry-related deficiencies in the petitioner's original 12/11/03 submission. These deficiencies were communicated to zuChem in your letter dated 5/5/04. ZuChem responded to the request for additional information in a 6/17/04 submission, and a 7/19/04 clarification.

Each request from the 5/5/04 letter is summarized below, followed by a discussion of zuChem's response.

1. Mannitol specifications

In their original submission, zuChem had provided data demonstrating the compliance of their mannitol product with the Food Chemicals Codex, 4th edition (FCC IV) specifications. However, the regulation for mannitol, 21 CFR 180.25(b), requires compliance with the mannitol specifications listed in the Food Chemicals Codex, 3rd edition (FCC III), not FCC IV. As a result, we had requested verification that mannitol produced by zuChem's fermentation process would meet the FCC III specification for arsenic (not more than 3 mg/kg (ppm)). We also requested a general statement from zuChem assuring that mannitol produced by their manufacturing technique would meet all FCC III specifications.

ZuChem states in their 6/17/04 submission that they are confident that mannitol produced by their fermentation process would conform to FCC III specifications. They also state that they have no reason to believe that arsenic would be present in mannitol produced by their method at levels exceeding those currently found in commercially available mannitol. Rather than provide analytical data to demonstrate this, they have provided a list of the possible sources of arsenic contamination (raw materials, equipment, equipment cleaning, packaging, and access to manufacturing areas) and described how their process would not be susceptible to contamination from these factors. ZuChem also states that mannitol produced using their fermentation method undergoes a . process which is highly effective

000595

at removing impurities including arsenic.

We are satisfied with zuChem's response, and believe that mannitol produced by their fermentation process would conform to FCC III specifications.

2. Presence of other sugar alcohols

ZuChem was requested to comment on the presence of sugar alcohols other than mannitol in their product, and to provide a discussion regarding the comparison of sugar alcohol levels in their product with those in commercially available mannitol.¹

In their 6/17/04 submission, zuChem stated that mannitol produced with their fermentation method is equivalent to commercially available mannitol with regard to the presence of sugar alcohols other than mannitol. In this submission, zuChem also reported that analytical testing had been performed on five representative batches of mannitol to test for the presence of sorbitol, maltitol, lactitol, xylitol, and, in a separate study, arabitol. However, actual data were not provided, and it was not clear if the referenced studies were new, or had previously been submitted. In the 7/19/04 submission, zuChem verified that the data were new, and provided chromatograms from the high performance liquid chromatography (HPLC) analyses.² ZuChem's 7/19/04 submission contains a report (dated 7/7/04) that states that sorbitol, maltitol, lactitol and xylitol were not detected at a limit of detection (LOD) of 0.01%, and a report (dated 7/15/04) that states that arabitol was not detected at a LOC of 0.05%.

We concur with zuChem's analysis.

3. Summary

We have no further questions. The petition is suitable for regulation with regard to the chemistry information.



Daniel E. Folmer, Ph.D.

¹ In our 4/20/04 chemistry memorandum (see "Other sugar alcohols"), we stated that mannitol produced by the petitioner's method appeared to contain sorbitol according to high performance liquid chromatography (HPLC) chromatograms (labeled 'mannitol') submitted by the petitioner in Appendix D of the original 12/11/03 submission. It is now apparent, based on information in zuChem's 7/19/04 submission, that the chromatograms showing the presence of sorbitol were, in fact, chromatograms of a mannitol reference standard. The data representing lots of zuChem's mannitol (labeled 2003-53680, 2003-53681, 2003-53682, 2003-53683, and 2003-53684) in zuChem's original submission do not show the presence of other sugar alcohols.

² Although the data are new, the same sample lots were analyzed as in the original 12/11/03 submission.

000596