~~MAY 17 1991~~ CSO

SUCRALFATE SUSPENSION
Carafate™ 1 Gram/10mL
Amendment to NDA 19-183
Reviewer: Lydia C. Kaus Boggs, MS, PhD
PC

Marion Laboratories, Inc.
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Submission Date:
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APR 11 1991

REVIEW OF DISSOLUTION METHOD

Background:
Sucralfate consists of a basic aluminum salt of sucrose octasulfate and is used in the treatment of gastric and duodenal ulcers.The sucralfate molecule can be considered to contain eight $Al_2(OH)_5$ ions complexed to a sulfated disaccharide skeleton. The $Al_2(OH)_5$ groups dissociate at gastric pH, resulting in a negatively charged molecule which polymerizes. This polymerized sucrose octasulfate adheres with greater affinity to damaged mucosa.

The firm has been asked to develop a dissolution method since the NDA approval of the tablets. This dissolution test is concerned with measuring soluble aluminum released and although this has not been shown to reflect the local availability of the pharmacologically active species, the method gives an indication of the extent of molecular dissociation at low pH. The dissolution method would also be an additional assurance of quality control.

The amendment to NDA 19-183, Submitted August 10th, 1990 was a proposal for a dissolution method to measure aluminum release from the suspension and to set a specification.

Initial proposal:

Final proposal:
900mL 0.1N HCl 37°C USP(II) Paddle @ 75rpm , NLT . _ aluminum released at 30 minutes.

The firm justified the change by saying that the increased speed improves the dispersal of the contents in the dissolution vessel and the changes "improve the ruggedness of the test method". The quoted remark needs to be expanded. The results using the two methods were compared by observation alone: no statistical comparison was offered.

The following comments were made by the reviewer in the review of the August 10th, 1990 submission:
Comments:
1. Statistical comparison needs to be made between the two methods proposed for dissolution specification.

2. At least twelve samples from each lot should be analyzed and presented not just one sample

per lot. This will give some indication of variance within the lot.

3. A full profile of mg aluminum released against individual time points is required for the final proposed specification for each of the lots tested. This should be expressed as % aluminum released of the total aluminum present in the 1 gram sucralfate dose.

The final specification and method will be set once the information requested above has been forwarded to the Division.

4. There needs to be some further developmental work for *in vitro* tests that more closely relate to the pharmacological action of the active species. There is also some *in vivo* work required which can relate mg of aluminum released in the stomach to actual aluminum measured in the plasma. These studies would be designed under consult from the clinicians. The Division looks forward to receiving this information from the firm.
Note: HFD-180 only forwarded Comments 1 to 3 to the firm.

Response:
Reviewer's question:
1. You have proposed two different methods for dissolution specification. Please provide a statistical comparison between the two methods.

The firm's response:
"Method M1226 is the only method that we have proposed for measuring the aluminum release of Carafate Suspension. After gaining additional experience with aluminum release testing, two changes were suggested to fine-tune the existing method.

The first point was that careful control of the pH led to improved precision. The method was revised so that the starting pH was monitored, and adjusted if it was incorrect.

The second point was that the dissolution testing of a dose of suspension is more exacting than the dissolution testing of a tablet. The aluminum release profile of the suspension depends on the manner or "style" of introduction of the suspension to the dissolution fluid. Unlike a tablet, a sample of suspension is quickly dispersed throughout the dissolution fluid. Additional experience with different operators showed that the test results were partially operator dependent. The aluminum release curves were very dependent on whether the operator quickly "injected" or slowly "drained" the suspension into the dissolution fluid. To make a more robust test method that could be reproduced by different operators in different laboratories, the paddle speed was increased. The change in rotation rate produced the desired result and made the method more rugged, but it also changed the curves, which showed a more rapid aluminum release profile. In order to compensate for this, the sampling point was advanced from 60 to 30 minutes."

The firm's response is acceptable.

2. In order to demonstrate variance between lots, you should analyze at least 12 samples from each lot, not just one.

3. You should provide a full profile of the amount of aluminum released (in mg) against individual time points for the final proposed specification for each of the lots tested. You should express this as per cent aluminum released of the total aluminum present in the 1 gram sucralfate dose.

The firm's response:
"In order to demonstrate variance between lots, 12 bottles were tested for each of four lots of Carafate Suspension. As discussed in our 3-15-91 phone conversation, only lots which were within the proposed expiration date of 36 months, or just recently expired, were assayed."

The data submitted can be summarized:

Mean of 12 Samples of Aluminum Release for Carafate Suspension

Lot Number	0.25 h	0.5 h	0.75 h	1 h
K02401 Full Scale Al in 10mL=193 mg	127 mg =66% Al (%CV 3%)	144 mg =75% Al (%CV 3%)	147 mg =76% Al (%CV 3%)	152 mg=79% Al (%CV 3%)
K02948 Full Scale Al in 10mL=188 mg	130 mg =69% Al (%CV 6%)	145 mg =76% Al (%CV 6%)	144 mg =76% Al (%CV 5%)	144 mg =76% Al (%CV 5%)
K02949 Full Scale Al in 10mL=188 mg	138 mg =73% Al (%CV 4%)	149 mg =79% Al (%CV 4%)	154 mg =82% Al (%CV 3%)	155 mg =82% Al (%CV 3%)
PD038713 Pilot/Clinical Al in 10mL=193 mg	116 mg =60% Al (%CV 1%)	149 mg =77% Al (%CV 1%)	154 mg =80% Al (%CV 1%)	157 mg =81% Al (%CV 1%)

The firm's proposal:
900mL 0.1N HCl 37°C USP(II) Paddle @ 75rpm , NLT aluminum released at 30 minutes.

The proposed dissolution specification should be set at:
900mL 0.1N HCl 37°C USP(II) Paddle @ 75 rpm, NLT of total aluminum available for release at 30 minutes in 10mL (1G) of Carafate™ Suspension.

RECOMMENDATION

The firm has responded satisfactorily to the outstanding questions regarding an aluminum release specification for Carafate™ Suspension. The reviewer recommends the following specification to be set on the basis of the data submitted by the firm:

900mL 0.1N HCl 37°C USP(II) Paddle @ 75 rpm, NLT f total aluminum available for release at 30 minutes in 10mL (1G) of Carafate Suspension.

4/11/91

Lydia C. Kaus Boggs, MS, PhD.
Pharmacokinetics Evaluation Branch

FT Initialed by John Hunt 5/16/91

cc NDA 19-183(Amendment), HFD-180, HFD-426, Chron, Drug Files, HFD-19(FOI).
PC:LCKB:N19-183b:4-11-91

Table 1
Aluminum Release for Carafate Suspension Lot K02401
Full Scale Batch

0.25 Hour (mg Al)	0.5 Hour (mg Al)	0.75 Hour (mg Al)	1 Hour (mg Al)
(b) (4)			
cv = 3%	cv = 3%	cv = 3%	cv = 3%
Avg. (mg) = 127	Avg. (mg) = 144	Avg. (mg) = 147	Avg. (mg) = 152
Al released = (b) (4)%	Al released = (b) (4)%	Al released = (b) (4)%	Al released = (b) (4)%

Table 2
Aluminum Release for Carafate Suspension Lot K02948
Full Scale Batch

0.25 Hour (mg Al)	0.5 Hour (mg Al)	0.75 Hour (mg Al)	1 Hour (mg Al)
(b) (4)			
cv = 6%	cv = 6%	cv = 5%	cv = 5%
Avg. (mg) = 130	Avg. (mg) = 145	Avg. (mg) = 144	Avg. (mg) = 144
Al released = (b) (4)%	Al released = (b) (4)%	Al released = (b) (4)%	Al released = (b) (4)%

Table 3
Aluminum Release for Carafate Suspension Lot K02949
Full Scale Batch

0.25 Hour (mg Al)	0.5 Hour (mg Al)	0.75 Hour (mg Al)	1 Hour (mg Al)
(b) (4)			
cv = 4%	cv = 4%	cv = 3%	cv = 3%
Avg. (mg) = 138	Avg. (mg) = 149	Avg. (mg) = 154	Avg. (mg) = 155
Al released = (b) (4)%	Al released = (b) (4)%	Al released = (b) (4)%	Al released = (b) (4)%

Table 4
Aluminum Release for Carafate Suspension Lot PD038713
Pilot Size Batch/Clinical Lot

0.25 Hour (mg Al)	0.5 Hour (mg Al)	0.75 Hour (mg Al)	1 Hour (mg Al)
(b) (4)			
cv = 1%	cv = 1%	cv = 1%	cv = 1%
Avg. (mg) = 116	Avg. (mg) = 149	Avg. (mg) = 154	Avg. (mg) = 157
Al released = (b) (4)%	Al released = (b) (4)%	Al released = (b) (4)%	Al released = (b) (4)%

Table 5
Aluminum Contents for Carafate Suspension

Lot Number	Aluminum Content (mg/10 mL)
K02401	193
K02948	188
K02949	188
PD038713	193

Figure 1
Aluminum Release
CARAFATE SUSPENSION
75 rpm

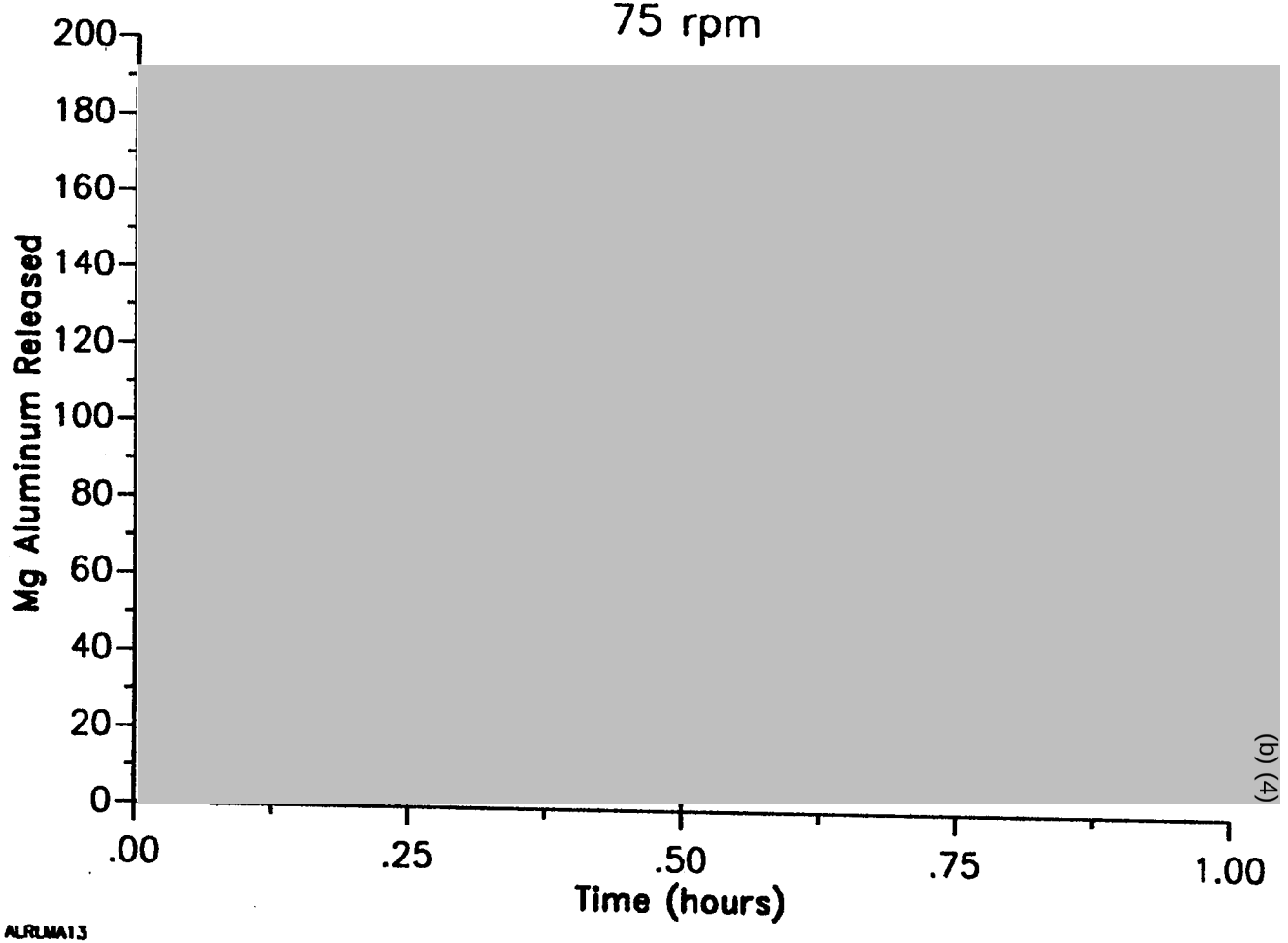

Figure 2
Aluminum Release
CARAFATE SUSPENSION
75 rpm