CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020745

STATISTICAL REVIEW(S)

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STATISTICAL REVIEW AND EVALUATION STABILITY STUDY

Date: FEB 7 1997

NDA#	20-745	
Applicant:	Glaxo Wellcome Inc.	
Name of Drug:	Zantac 75 EFFERdose Tablets (ranitidine hydrochloride)	
Documents Reviewed:	January 28, 1997	
Statistical Reviewer:	Moh-Jee Ng	(HFD-715)
Chemist:	Dr. Sieczkowski	(HFD-180)

FEB 7 1997

Summary

. The sponsor proposed a 24-month expiry date based on 18-months of data for Zantac 75 EFFERdose (ranitidine hydrochloride) tablets for over-the counter use stored between 2°C/AMBH and 30 C/60%RH.

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. The proposed twenty four month expiration date is supported by these data using both the sponsor's analysis and the analysis in this review.

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I. Introduction

In this amendment, the sponsor submitted updated stability data and requested a shelf-life of 24 months for 2°C/Ambient Humidity and 30°C/60% Relative Humidity.

II. Sponsor's Design and Analyses

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In this stability study, two stability storage conditions were used 1) 2°C/AMBH and 2) 30°C/60% RH. Two tests were performed 1) assay for Ranitidine content and (2) assay for Total drug-related impurities by The specification limits for the tests were 1) of label claim (67.5 and 82.5 mg/tablet, respectively) and ranitidine content. The three batches were GFD30005, GFD30006 and GFD30007. The test intervals were 0, 2,4,6, 9, 12 and 18 months.

The data was provided by the sponsor on a 3.5 floppy diskette. The statistical method used by the sponsor in accordance with the FDA's 'Guidelines for Submitting Documentation for the Stability of Human Drugs and Biologics" (February 1987). Results were summarized in the appendix. The sponsor proposed a 24 month shelf-life for Zantac 75 EFFERdose tablets for over-the-counter used when stored between 22°C/AMBH and 30°C/60% RH.

III. Review's Analysis

Methods

The reviewer used the FDA PC/STAB program written by Moh-Jee Ng to analyze the data. The statistical foundation of the program was documented in the 1987 "Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics". STAB consists of the following two steps:

Step 1: Model selection (tests for pooling of stability batch data)

A statistical test is performed to determine whether or not the degradation curves, considering all individual batch separately, are similar. If the degradation curves are similar, it is desirable to pool the data in order to obtain more precise estimates of expiration dating periods. Batch similarity of the degradation curves is assessed by fitting linear regression models to the data, and applying statistical tests for equality of slopes and/or zero-time intercepts to these models. The following two conditions must be satisfied to allow such pooling of the data.

a) Equality of slopes: To test whether a model with separate intercepts and separate slopes fits the data better than a model with separate intercepts and common slope. A p-value of 0.25 or greater is required to support the hypothesis that all regression lines have a common slope.

b) Equality of intercepts given equal slopes: To test whether a model with separate intercepts and the estimated common slopes fits the data better than a model with common intercept and common slope. A p-value of 0.25 or greater is required to support the hypothesis that all regression lines have a common intercept.

The rationale for using p-value of 0.25 for tests of this nature is presented by Bancroft in "Analysis and inference for incompletely specified models involving the use of preliminary test of significance", Biometrics, pp. 427-442 (1964).

Based on the results of step 1, one of the following models is selected for the degradation curve estimation:

a) separate intercepts and separate slopes,
b) separate intercepts and common slope,
c) common intercept and common slope.

Step 2: Construction of lower and upper limits of 95% confidence intervals for the mean degradation curve.

The lower and/or upper limits of the 95% confidence bands are constructed for the mean degradation curve based on the method selected in step 1.

Acceptable Criteria

In order to have an acceptable level of a variable under test, with 95% confidence coverage, the lower confidence bound should be above the lower specification limit and the upper confidence bound should be below the upper specification limit when both upper and lower specification limits are required. However, if only one specification limit is needed, then neither the lower confidence bound should be above the lower specification limit or the upper confidence bound should be below the upper specification limit with 95% confidence coverage.

Data analyses and results

The stability data submitted by the sponsor were analyzed. The results are presented for each variable.

1. Ranitidine Content (% of Label Claim)

Storage condition: 2°C/Ambient Humidity

The p-value of statistical tests for the selection of degradation model are presented in Table 1. Based on these p-values a model with separate intercepts and common slope was selected. The degradation lines, lower and upper 95% confidence bounds were calculated. The estimated degradation lines along with the lower and upper 95% confidence bounds are presented in Figure 1a, 1b and 1c.

The results of the analysis support an expiration dating period of 24 months at 2°C/Ambient Humidity.

Table 1
Analysis of Variance Table

SOURCE	SS	DF	MS	F	P
A	24.88	4	6.22	7.0554	0.00211
B	24.49	2	12.24	13.8897	0.00039
C	0.39	2	0.19	0.2212	0.80416
D	13.22	15	0.88		
E	209166.19	6	34861.03		

Batch	Fitted Line	Expiration date
GFD30005	Y = 99.352159468 + -0.024806202 X	72
GFD30006	Y = 101.49501661 + -0.024806202 X	72
GFD30007	Y = 99.080730897 + -0.024806202 X	72

Storage condition: 30°C/60%RH

The p-value of statistical tests for the selection of degradation model are presented in Table 2. Based on these p-values a model with separate intercepts and separate slopes was selected. The degradation lines, lower and upper 95% confidence bounds were calculated. The estimated degradation lines along with the lower and upper 95% confidence bounds are presented in Figure 1d, 1e and 1f.

The results of the analysis support an expiration dating period of 24 months at 30°C/60% RH.

Table 2
Analysis of Variance Table

SOURCE	SS	DF	MS	F	P
A	37.11	4	9.28	15.8013	0.00003
B	35.30	2	17.65	30.0577	0.00001
C	1.81	2	0.91	1.5449	0.24543
D	8.81	15	0.59		
E	207693.49	6	34615.58		

Batch	Fitted Line	Expiration date
GFD30005	Y = 99.625458996 + -0.148592411 X	33
GFD30006	Y = 102.43072215 + -0.159118727 x	45
GFD30007	Y = 98.837086903 + -0.04626683 X	72

2. Total Drug-Related impurities by TLC (Total Impurities)

Storage condition: 2°C/Ambient Humidity

The p-value of statistical tests for the selection of degradation model are presented in Table 3. Based on these p-values a model with common intercept and common slope was selected. The degradation lines and upper 95% confidence bounds were calculated. The estimated degradation lines along with the upper 95% confidence bounds are presented in Figure 1g .

The results of the analysis support an expiration dating period of 24 months at 2°C/Ambient Humidity.

Table 3
Analysis of Variance Table

SOURCE	SS	DF	MS	F	P
A	0.00890	4	0.00222	0.12755	0.97011
B	0.00095	2	0.00048	0.02730	0.97312
C	0.00795	2	0.00397	0.22779	0.79899
D	0.26162	15	0.01744		
E	4.25838	6	0.70973		

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Batch	Fitted Line	Expiration date
3 batches	Y = 0.3912892697 + 0.0077315381 X	72

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Storage condition: 30°C/60%RH

The p-value of statistical tests for the selection of degradation model are presented in Table 4.Based on these p-values a model with common intercept and separate slopes was selected. The degradation lines and upper 95% confidence bounds were calculated. The estimated degradation lines along with the upper 95% confidence bounds are presented in Figure 1h.

The results of the analysis support an expiration dating period of 24 months at 30°C/60% RH.

Table 4
Analysis of Variance Table

SOURCE	SS	DF	MS	F	P
A	0.01579	4	0.00395	0.31404	0.86413
B	0.00095	2	0.00048	0.03788	0.96292
C	0.01484	2	0.00742	0.59020	0.56659
D	0.18854	15	0.01257		
E	7.28146	6	1.21358		

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Batch	Study Fitted Line	Expiration date
for 3 batches	Y = 0.4269685843 + -0.0204814361 X	41

IV. Conclusion

Supports, on the 18-months of stability data, an expiration dating period of 24 months for Zantac 75 EFFERdose (ranitidine hydrochloride) tablets for over-the-counter use stored between 2°C/AMBH and 30 C/60%RH.

/S/

Mon-Jee Ng
Operation Research Analyst

Concur: Dr. Huque /S/ 2/4/97
Dr. Smith /S/ 2/6/97
Dr. Nevius /S/ 2-6-97

cc:
Orig. NDA 20-164
HFD-180/ Division Files
HFD-180/ Dr. Fredd
HFD-180/ Mr. Folkendt
HFD-180/ Dr. Sieczkowski
HFD-720/ Dr. Smith
HFD-720/ Dr. Huque
HFD-715/ Division File, Chron
HFD-715/ Dr. Nevius, Ms. Ng

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information

Minutes of telecon
2/24/98

NDA 20-745 /S/

FDA participants: Michael Folkendt, PM /S/
Sakineh Walther, PM
Rosemary Cook, SPM

and:

Glaxo Wellcome participants:
Ms. Sara Armentrout, Regulatory Affair Specialist.

NDA 20-745, provides for an alternate dosage form for nonprescription ranitidine hydrochloride. An approval letter (AE) pending labeling revisions was issued to this application on July 8, 1997. Upon the review of the subsequent revised draft labeling, approval of this application, with additional labeling revisions, was recommended.

This call was initiated to obtain applicant's agreements to the following labeling revisions to be included in the approval letter:

1. Delete the word "quickly" from the second sentence of the first bullet statement on the front of the package insert.

2. Within 6 months or at the next printing of the labeling, whichever comes first:

   a. Revise the directions to state "Dissolve 1 EFFERdose® tablet completely in a full glass of water."

   b. Add a section titled "Tips for Managing Heartburn" with the following bullet statements to the package insert:

- Do not lie flat or bend over soon after eating.
- Do not eat late at night, or just before bedtime.
- Avoid foods or drinks that are more likely to cause heartburn, such as rich, spicy, fatty, and fried foods, chocolate, caffeine, alcohol, and even some fruits and vegetables.
- Eat slowly and do not eat big meals.
- If you are overweight, lose weight.
- If you smoke, stop or cut down smoking.
- Raise the head of your bed.
- Avoid wearing tight clothing around your stomach.

Ms. Armentrout agreed to these changes.

cc:
Archival NDA 20-745
HFD-180 Div. File
HFD-180/CSO/M.Folkendt
HFD-560 Div. File
HFD-560/PM/S. Walther

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