CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-906

STATISTICAL REVIEW(S)

CHAPMAN

Statistical Review and Evaluation

NDA#: 20-906

DEC 18 1997

APPLICANT: Bristol-Myers Squibb

NAME OF DRUG: Etopophos (etoposide phosphate) for Injection

DOCUMENTS REVIEWED: Amendment Dated 09/11/97, Pages 1-9.

CHEMISTRY REVIEWER: Robert Barron, Ph.D.

1. Background

This is the sponsor's response to information requested by this reviewer on 7/18/97. A diskette containing the stability data of four batches was also included. Dr. R. Barron (HFD-150) requested a statistical review of the sponsor's submission.

2. Sponsor's Results

The sponsor explained that the 12-month stability report contained the stability data in actual potency values and in percent initial but their statistical analysis had been done in the actual potency values. They insisted on using two-sided 90 % confidence limits around the regression lines based on the ICH stability guidelines. This reviewer had requested 95 % confidence bands to maintain consistency across reviews. Finally, the sponsor provided an updated regression analysis including the potential outlier value for batch S95E1008 at one month.

The sponsor estimated the expiration dating period by constructing a line with an intercept of 95 % label claim and a slope being equal to the lower 95 % confidence limit of the slope estimate obtained from the data. The intersection of this line with the lower specification limit occurred after 36 months and it was concluded that the product would be stable for this time when stored under refrigeration and protected from light.

3. Reviewer's Results

The sponsor's use of actual potency values in their analysis is equivalent to using percent label claim values and is therefore acceptable.

It has been the practice of the Division of Biometrics I to form two-sided 95 % confidence bands around the regression line(s). It is true, that these lines correspond to one-sided 97.5 % confidence bands and will result in shorter expiration dating periods. In order to remain consistent with previous reviews, this Division requested the use of two-sided 95 % confidence bands. For the submission at hand, the point is academic as the potency assays appear to be very stable and predict a long expiry period with either approach.

The sponsor complied with including a potential outlier value into the analysis, but their approach to setting an expiration dating period does not follow the FDA Guideline. Rather than forming the first intersection of the two-sided 95 % confidence bands around the regression line(s) with the specification limits, the sponsor calculated the lower 95 % confidence limit of the common slope estimate and formed a line with this slope and an artificial intercept of 95 % label claim. Using a minimum specification limit of 90 %LC, an expiry period of more than 36 months (actually 4.7 years) was estimated. Using the approach as outlined in the FDA Guideline, this reviewer could not exactly verify the sponsor's p-values for common slope or common intercept but could reproduce the intercept and slope estimates to one and three significant digits, respectively. The minor observed differences are not clear to this reviewer. It is possible that the sponsor's test for poolability of intercepts was non-conditional and also their computations were based on mean observations whereas this reviewer used a conditional test for the intercept (given a common slope) and the individual assay values in the analysis. There was no difference in the adoption of the model (parallel lines) nor in the general conclusion that the product can be expected to remain within the specification limits for well beyond the observed times. This reviewer's estimated expiration dating periods were more than 84 months.

The sponsor was also requested to provide regression analysis for the fastest forming degradation product. They used the same approach as for the potency assay data. This reviewer's re-analysis resulted in a single regression line for the data of the four batches. Based on the submitted data, etoposide can be expected to remain below the 3 % level for well beyond the observed 18 and 24 months data. The upper confidence band had not yet crossed the specification limit at 84 months. Again, there were small numeric differences with the sponsor's results, but their consequence was immaterial .

4. Summary and Conclusion

This reviewer did not agree with the sponsor's statistical approach in setting the expiry periods. In this reviewer's re-analysis it was confirmed that the estimated expiration dating periods (84 months) for the potency assay and the etoposide impurity reach well beyond the observed data of 18 and 24 months.

The other issues raised with the sponsor were satisfactorily answered except that the sponsor insisted on using 90 % confidence limits based on ICH Guideline, rather than the 95 % confidence limits requested by this Division. This reviewer used the 95% confidence limits.

/S/

Roswitha E. Kelly
Mathematical Statistician

Concur: /S/ 12/16/97

Tony Koutsoukos, Ph.D.
Acting Team Leader

/S/ 12/18/97

George Chi, Ph.D.
Director, DB I

cc:
Archival NDA 20-906, Etopophos (etoposide phosphate) for Injection, Bristol-Myers Squibb
STABILITY

HFD-150/Division File
HFD-150/Dr. Liang
HFD-150/Dr. Barron
HFD-150/~~Ms. Spillman~~ Chapman
HFD-344/Dr. Barton
HFD-700/Dr. Fairweather
HFD-710/Dr. Koutsoukos
HFD-710/Ms. Kelly
HFD-710/Dr. Chi
HFD-710/Chron\12/15/97

This review consists of 3 pages.
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BAILAR

Statistical Review and Evaluation

DATE: OCT 31 1997

NDA#: 20-906

APPLICANT: Bristol-Myers Squibb

NAME OF DRUG: Etopophos (etoposide phosphate) for Injection

DOCUMENTS REVIEWED: Amendment Dated 09/11/97

1. Background

This is the sponsor's response to information requested by this reviewer on 7/18/97. A diskette containing the stability data of four batches was also included. Dr. R. Barron (HFD-150) requested a statistical review of the sponsor's submission.

2. Sponsor's Results

The sponsor explained that the 12-month stability report contained the stability data as actual potency values and as percent initial but that their statistical analysis had been done in the actual potency values. They insisted on using two-sided 90 % confidence limits around the regression lines based on the ICH stability guidelines. This reviewer had requested 95 % confidence bands to maintain consistency across reviews. Finally, the sponsor provided an updated regression analysis including the potential outlier value for batch S95E1008 at one month.

Using an intercept of 95 % label claim and the lower 95 % confidence limit of the slope estimate, the sponsor predicted an expiration dating period of more than 36 months when the product was stored under refrigeration and protected from light.

3. Reviewer's Results

The sponsor's use of actual potency values in their analysis is equivalent to using percent label claim values and is therefore acceptable.

It has been the practice of the Division of Biometrics I to form two-sided 95 % confidence bands around the regression line(s). It is true, that these lines correspond to one-sided 97.5 % confidence bands and will result in shorter expiration dating periods. In order to remain consistent with previous reviews this Division requested the use of the two-sided 95 % confidence bands. For the submission at hand the point is academic as the potency assays appear to be very stable and predict a long expiry period with either approach.

The sponsor complied with including a potential outlier value into the analysis, but their approach to setting an expiration dating period does not follow the FDA Guideline. Rather than forming the ealiest intersection of the two-sided 95 % confidence bands around the regressionline(s) with the specification limits, the sponsor calculated the lower 95 % confidence limit of the common slope estimate and formed a line with this slope and an artificial 95 % label claim intercept. Using a minimum specification limit of 90 %LC, an expiry period of more than 36 months (actually 4.7 years) was estimated. Using the approach as outlined in the FDA Guideline, this reviewer could not exactly verify the sponsor's p-values for common slope or common intercept but could reproduce the intercept and slope estimates to one and three significant digits, respectively. The minor

observed differences are not clear to this reviewer. It is possible that the sponsor's test for poolability of intercepts was non-conditional and also their computations were based on mean observations whereas this reviewer used a conditional test for the intercept (given a common slope) and the individual assay values in the analysis. There was no difference in the adoption of the model (parallel lines) and in the general conclusion that the product can be expected to remain within the specification limits for well beyond the observed times. This reviewer's estimated expiration dating periods were more than 84 months.

The sponsor was also requested to provide regression analysis for the fastest forming degradation product. They used the same approach as for the potency assay data. This reviewer's re-analysis resulted in a single regression line for the data of the four batches. Based on the submitted data, etoposide can be expected to remain below the 3 % level for well beyond the observed 18 and 24 months data. The upper confidence band had not yet crossed the specification limit at 84 months. Again, there were small numeric differences with the sponsor but their consequence was immaterial .

4. Summary and Conclusion

This reviewer did not agree with the sponsor's statistical approach in setting the expiry periods. In her re-analysis she did confirm that the estimated expiration dating periods (84 months) for the potency assay and the etoposide impurity reach well beyond the observed data of 18 and 24 months.

The other issues raised with the sponsor were satisfactorily answered except that they insisted on using 90 % confidence limits based on ICH Guideline, rather than the 95 % confidence limits requested by this Division. In her re-analysis this reviewer used the 95% confidence limits.

/S/

Roswitha E. Kelly
Mathematical Statistician

Concur: /S/ 10/27/97

Clare Gnecco, Ph.D.
Team Leader

/S/ 10/31/97

George Chi, Ph.D.
Director, DB I

cc:
Archival NDA 20-906, Etopophos (etoposide phosphate) for Injection, Bristol-Myers Squibb

STABILITY

HFD-150/Division File
HFD-150/Dr. Tolygesi
HFD-150/Dr. Barron
HFD-150/Ms. ~~Spilman~~ Chapman
HFD-344/Dr. Barton
HFD-700/Dr. Fairweather
HFD-710/Dr. Gnecco
HFD-710/Ms. Kelly
HFD-710/Dr. Chi
HFD-710/Chron\10/21/97

This review consists of 4 pages.
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-906

MICROBIOLOGY REVIEW(S)

SPILLMAN

JAN 12 1998

REVIEW FOR HFD-150
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGIST'S REVIEW #1 OF NDA

January 6, 1998

A. 1. NDA 20-906

SPONSOR Bristol-Myers Squibb

2. PRODUCT NAMES: ETOPOPHOS® (Etoposide Phosphate) for Injection

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 60 cc vial containing 500 mg, or a 100 cc vial containing 1000 mg of drug product, and both sizes are sealed with a stopper: this is a Pharmacy Bulk Package. The product is to be reconstituted and is then further diluted into parenteral fluid for infusion.

4. METHOD(S) OF STERILIZATION:

5. PHARMACOLOGICAL CATEGORY: Anti-neoplastic

6. DRUG PRIORITY CLASSIFICATION: 3S

B. 1. DATE OF INITIAL SUBMISSION: 25 February 1997

2. DATE OF AMENDMENTS: None

3. RELATED DOCUMENTS: The original submission was provided as a supplement to NDA 20-457. That NDA included letters of authorization to:

Document	Holder	Subject
DMF		
DMF		

4. ASSIGNED FOR REVIEW: 22 December 1997

C. REMARKS: The original submission was provided as a supplement to NDA 20-457. The supplement provided for multiple dose container systems of

These provisions exceed the USP23 <1> recommendations for Packaging and Storage, " *Unless otherwise specified in the individual monograph, no multiple-dose container contains a volume of Injection more than sufficient to permit the*

withdrawal of 30 mL." The product is not covered by a USP monograph. For these reasons the product was considered a pharmacy bulk package, and it was necessary to reclassify the submission as a new application. The NDA was refiled as NDA 20-906. New vial sizes, fill volumes and labeling were the key differences in the new product.

D. CONCLUSIONS: The submission is approvable for product quality microbiology issues.

/S/ 1-6-98

David Hussong, Ph.D.

1/12/98

cc:

Original NDA 20-906
HFD-160/Consult File
HFD-150/CSO/D. Spillman
HFD-150/Chemist/R. Barron
drafted by: D. Hussong, 01/06/98
R/D initialed by: P. Cooney

Filename: c:\d\nda\20-906r1.wpd