CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-448

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

NDA#: 20-448 Date: March 2, 1995

Applicant: McNeil Consumer Products Company

Name of drug: Imodium A-D (loperamide N-OXIDE) Chewable tablet, 2 mg

Documents reviewed: Original submission. Document dated 4/21/1994.

I. Introduction: In this NDA submission McNeil Consumer Products Company has requested for an expiration dating period of 24 months for Imodium A-D Chewable Tablet. Dr. George Chen, reviewing chemist, HFD-180 has requested the Division of Biometrics to perform statistical review and evaluation of the sponsor's stability data analyses.

After discussion with Dr. Chen, in this review, only the degradation data at 30 °C were used to perform the estimations of the expiration dates.

II. Design

Number of package types: 4

Package configurations:

Package Type I.:
Blisters - PVC/PA/PET/Foil/HSC -
PVC/PA/PET/Foil/HSC -

Package Type II.:
Pouch(NCR) - PA/LDPE/Foil/LDPE -

Package Type III.:
Pouch(CR) PET/LDPE/Foil/LDPE -
PET/LDPE/Foil/Plexar/nylon/Plexar-

Package Type IV.:
Vial - 20 mm Polypropylene -

Numbers of batches used: 4 - 7276, 7277, 7281, 7282 for Blisters;
3 - 7309, 7310, 7311 for Pouch
6 - 7304, 7305, 7306, 7307, 7308, 7314 for Pouch
3 - 7594, 7595, 7596 for Vial (only three batches used, suggested by the Chemist).

Tested Parameter:

Temperatures: 30°C.

Specification limits of loperamide : Not more than 2%.

Sampling times: For temperature 30° C, the observation time points for each package type are listed below.

Package Type	Batch#	Measurement Time(in months)
I	All four batches	0, 3, 6, 15, and 18
II	All three batches	0, 3, 6, 14, and 18
III	All six batches	0, 3, 6, 14, and 18
IV	7594, 7595, 7596	0, 8, 9, 12, and 18

III. Sponsor's analysis

The sponsor used the linear regression model to analyze the assay data. The averages of all 30°C assay results for individual time points were analyzed. If separate intercepts and/or slopes were recommended by the regression analysis for the batches used in each package type, then the model with the highest intercept value and/or most positive slope was employed to project the expiration period. From the statistical analysis, the sponsor declared that the batches for the four package types supported an expiration date of 24 months.

IV. Reviewer's analysis

Since package type I, Blisters, had two manufacturing sites and package type III, Pouch (CR), had two suppliers of materials, the reviewer first performed the covariance analysis with nested model to explore the effects of factors manufacturing site and material supplier on the estimations of the expiration dates for package type I and III, respectively. Then the linear regression analysis was used to estimate the expiration date for each package type.

i) Results of the covariance analysis

The models used for detecting the effects of factors manufacturing site and material supplier on the expiration dates for package type I and III were listed in Appendices I and II, respectively. The statistical results of the covariance analyses for package type I and III were presented in Table 1a, Table 1b, and Table 2a Table 2b, respectively.

Table 1a showed that the effect, AGE*MNFCTR, of manufacturer on the slope and the effect , AGE*BATCH(MNFCTR), of batch slope within manufacturer were non-significant for the first package typ (type I error equal to 0.4618 for AGE*MNFCTR and 0.6712 for AGE*BATCH(MNFCTR)), based on the significance level 0.25 set by the FDA guidline. Then, Model 2, deleting these two terms from Model 1, was employed to test the intercept effect, MNFCTR, induced by manufacturer on the expiration date for package type Blisters. Table 1b demonstrated that the intercept effect MNFCTR was significant (type I error equal to 0.051), based on the significance level 0.25 set by the FDA guidline. Therefore, only three batches, 7276, 7277, 7281, made from manufacturer American Mirrex will be used to project the expiration date for package type I.

Similarily, Table 2a showed that the effect, AGE*MATL, induced by the material on the slope were non-significant (type error equal to 0.9656), based on the significance level 0.25 set by the FDA guidline. Then, Model 4, deleting AGE*MATL from Model 3, was employed to test the intercept effect MATL, caused by the two different materials, on the expiration date for package type Pouch (CR). Table 2b indicated that the intercept effect MATL was not significant (type I error equal to 0.7392), based on the significance level 0.25 set by the FDA guidline. Since factor material did not resulted in a significant effects on the expiration date, the data form all six batches will be pooled to estimate the expiration date for the third package type.

Since the two SAS programs used to evaluate the levels of power for testing the effects MNFCTR and MATL on the expiration dates of the two package types are similar, only the one used for package type III was presented in Appendix II.

Following the FDA guideline, the type I significance levels used to evaluate the levels of power for the two package types were set at 0.25. The corresponding noncentral parameters for the two sided-tests were set as a function (COEF) of the ratio between the differences of two levels of the factor (manufacturer or material) and the model standard deviation. The evaluation results for package type I and III were listed in Tables 3 and 4, respectively.

Table 4 showed that the levels of power for both intercept and slope tests are high in general. Following the nonsignificant results in Table 2, the reviewer will use all six batches to estimate the expiration date for package type III.

ii) Linear regression analysis

The reviewer analyzed the stability data using the SAS program developed by the Division of

Biometrics, FDA. The procedures consist of the following two steps.

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

An assessment is made as to whether or not the degradation curves, considering all individual batches 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) The test of hypothesis that a model with separate intercepts and separate slopes (H_1) fits the data better than a model with separate intercepts and common slope (H_0) should have a p-value of 0.25 or greater, (equality of slopes) and,

b) The test of hypothesis that a model with separate intercepts and the estimated common slope (H_1) fits the data better than a model with common intercept and common slope (H_0) should have a p-value of 0.25 or greater (equality of intercepts given parallel lines).

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

At the end of step 1, one of the following models is selected for the degradation curves,

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

Step 2: Construction of the 95% lower, or 95% upper, or 95% two-sided confidence intervals for the mean degradation curve.

The 95% lower, or a 95% upper, or two-sided confidence intervals are constructed for the mean degradation curve based on model selected at step 1.

Acceptance criteria

In order to have an acceptable potency level of the assay under test, the 95 % lower confidence bound should be above the lower specification limit and the 95 % 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 either the 95% lower confidence bound should be above the lower specification limit or the 95% upper confidence bound should be below the upper specification limit.

Data analysis and results

There were four types of packages included in this study. The analysis performed in previous subsection i) suggested that only three batches, 7276, 7277, and 7281, made by manufacturer were to be used to estimate the expiration date for package type I. However, for the third package type, the statistical analysis results indicated that the data from two different material suppliers could be pooled to perform the estimation of the expiration date.

The analysis of variance for the selections of degradation models and the estimations of the expiration date for the four package types with room temperature 30°C are presented in Tables 5 thru 8, respectively. Based on the p-values in the analysis of variance table, model with separate interceptions and common slope for package type I, II, and IV was selected. However, model with separate intercepts and slopes was selected for package type III.

The bounds of 95% upper confidence intervals were calculated. The estimated degradation lines along with their 95% upper confidence bounds generating the shortest expiration dating periods for the package type I through type IV in room temperature 30°C are presented in Figures 1 thru 4, respectively.

The stability data of the loperamide for the four package types support an expiration dating period of 24 months (2 years) for Imodium A-D Chewable Tablet, 2mg. However, the estimated expiration date of 24 months can only be applied to Package type I manufactured at

V. Reviewer's comments

When model with separate intercepts and/or separate slope was selected, the sponsor used the highest intercept and/or most positive slope to project the expiration period. This method in general is not valid. Since the model with the highest intercept and/or most positive slope may have the narrower confidence bounds, the corresponding upper bound will provide a longer expiration date.

Based on the FDA guideline, If model with three regression lines for the three batches was selected, the regression model with the confidence bounds generating the shortest expiration period will be employed to project the expiration date.

VI. Summary

The sponsor submitted the stability data of loperamide on a diskette. There were four package types: type I through type IV. Stability of the loperamide was observed between 0 to 18 months. The results of reviewer's analyses on loperamide stability data for the four package types showed that the data supported the request for an expiration date

of 24 months for four package types listed in the subsection of Design. However, the expiration date of 24 months can only be applied to Package type I manufactured

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HFD-710/Chron
HFD-715/Dr. Lin
HFD-715/Dr. Chen
HFD-715/SARB Chron

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8 pages

Figure 1
Package Type I
Room Temperature 30°C

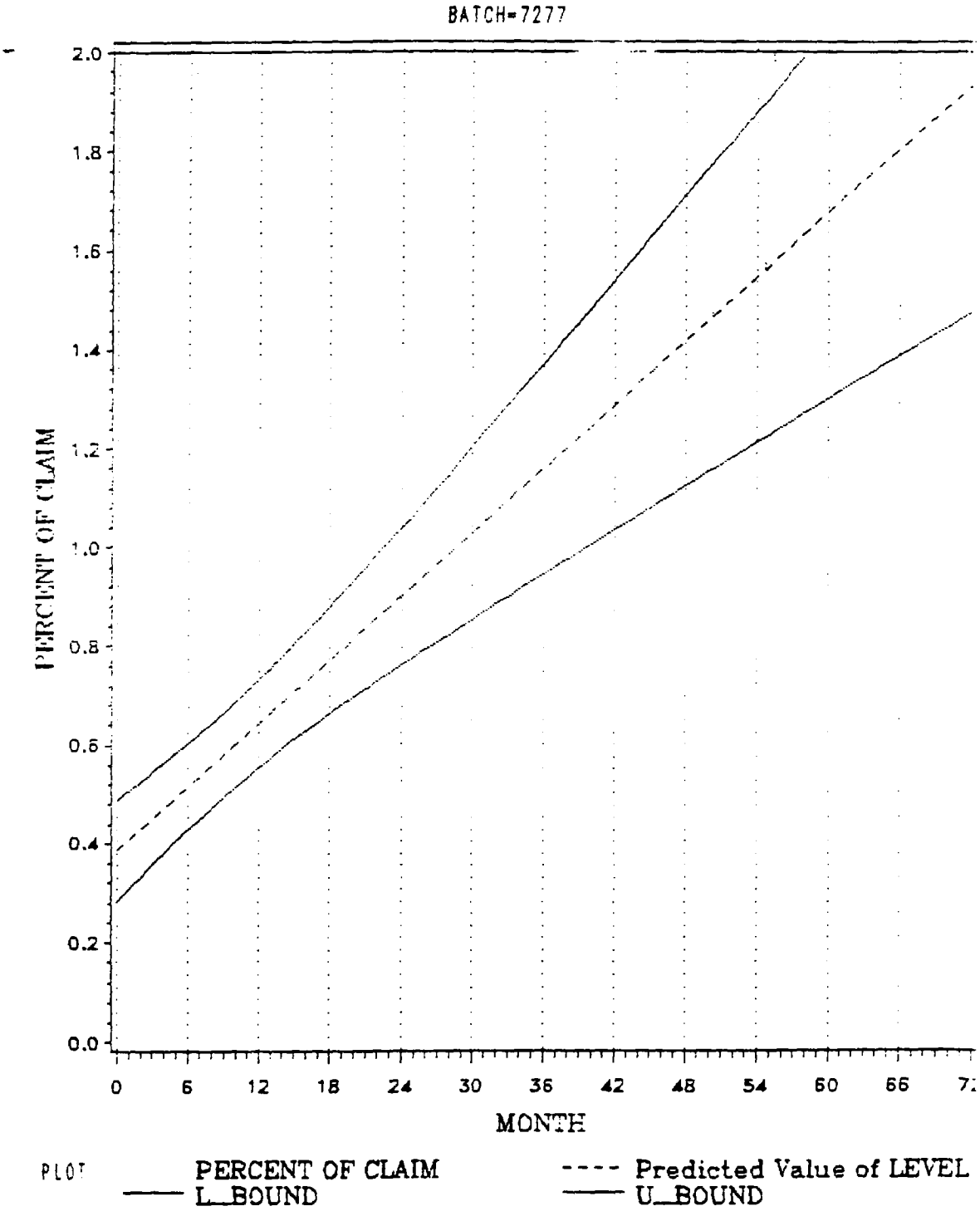


Figure 2
Package Type II
Room Temperature 30° C

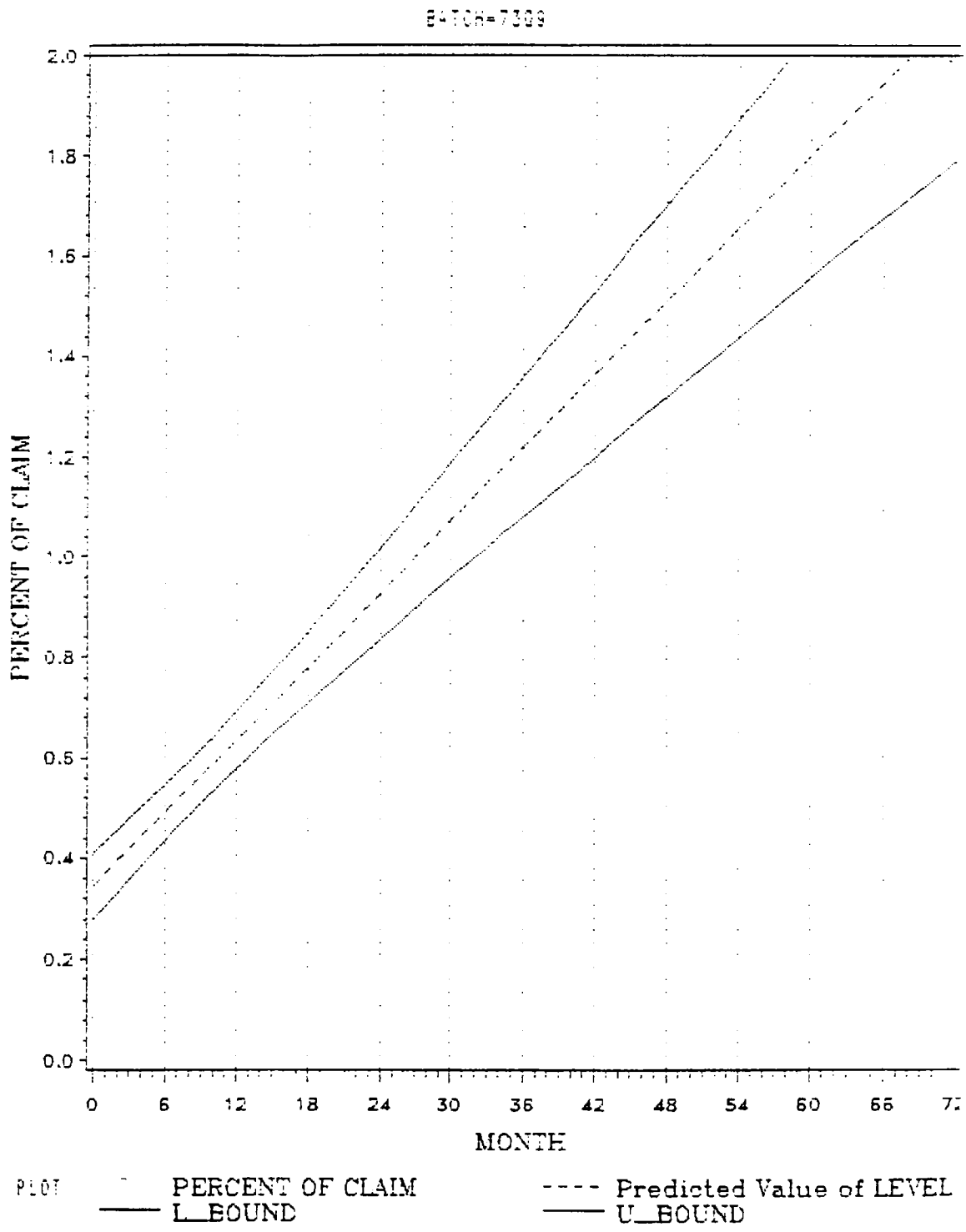


Figure 3
Package Type III
Room Temperature 30°C

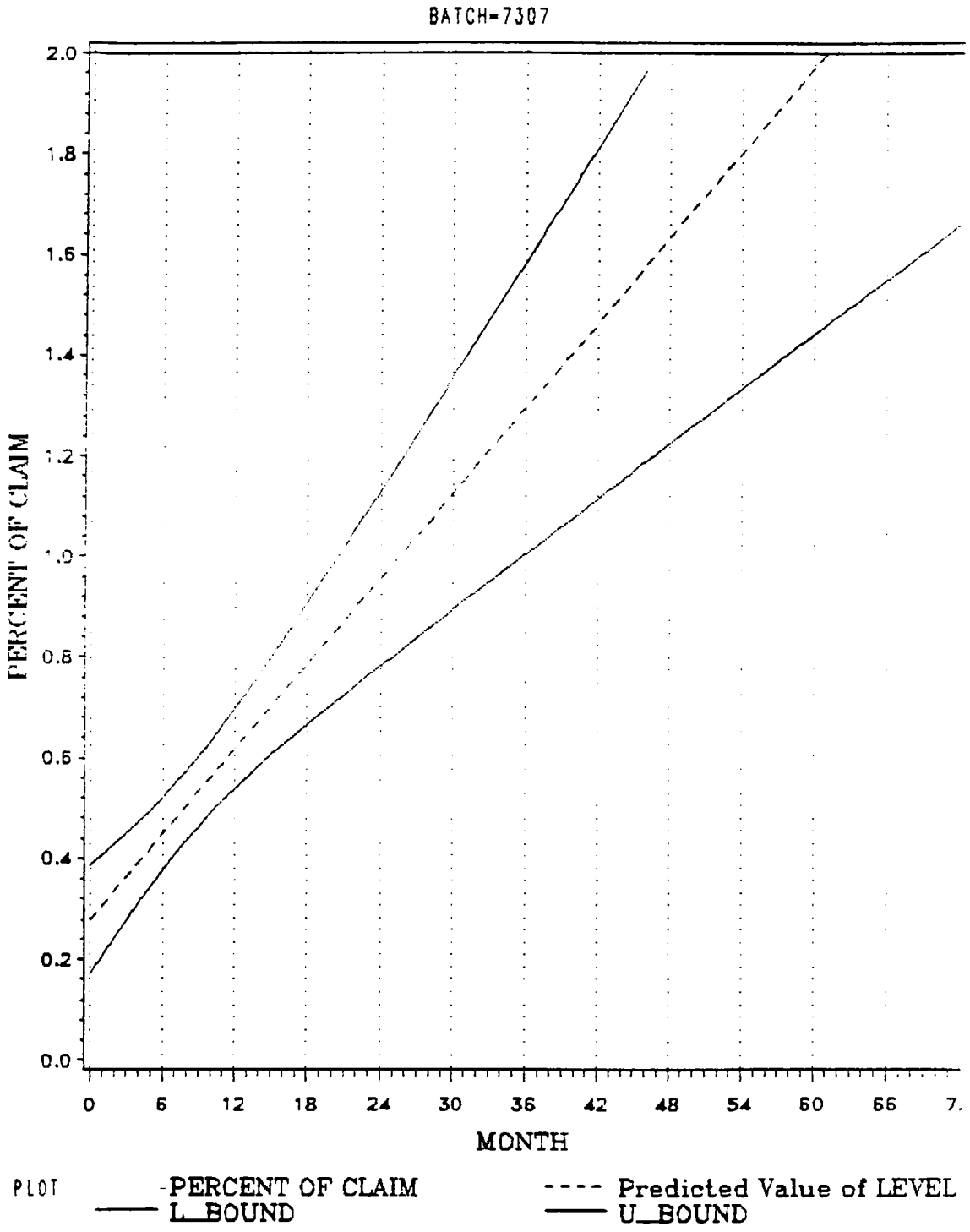
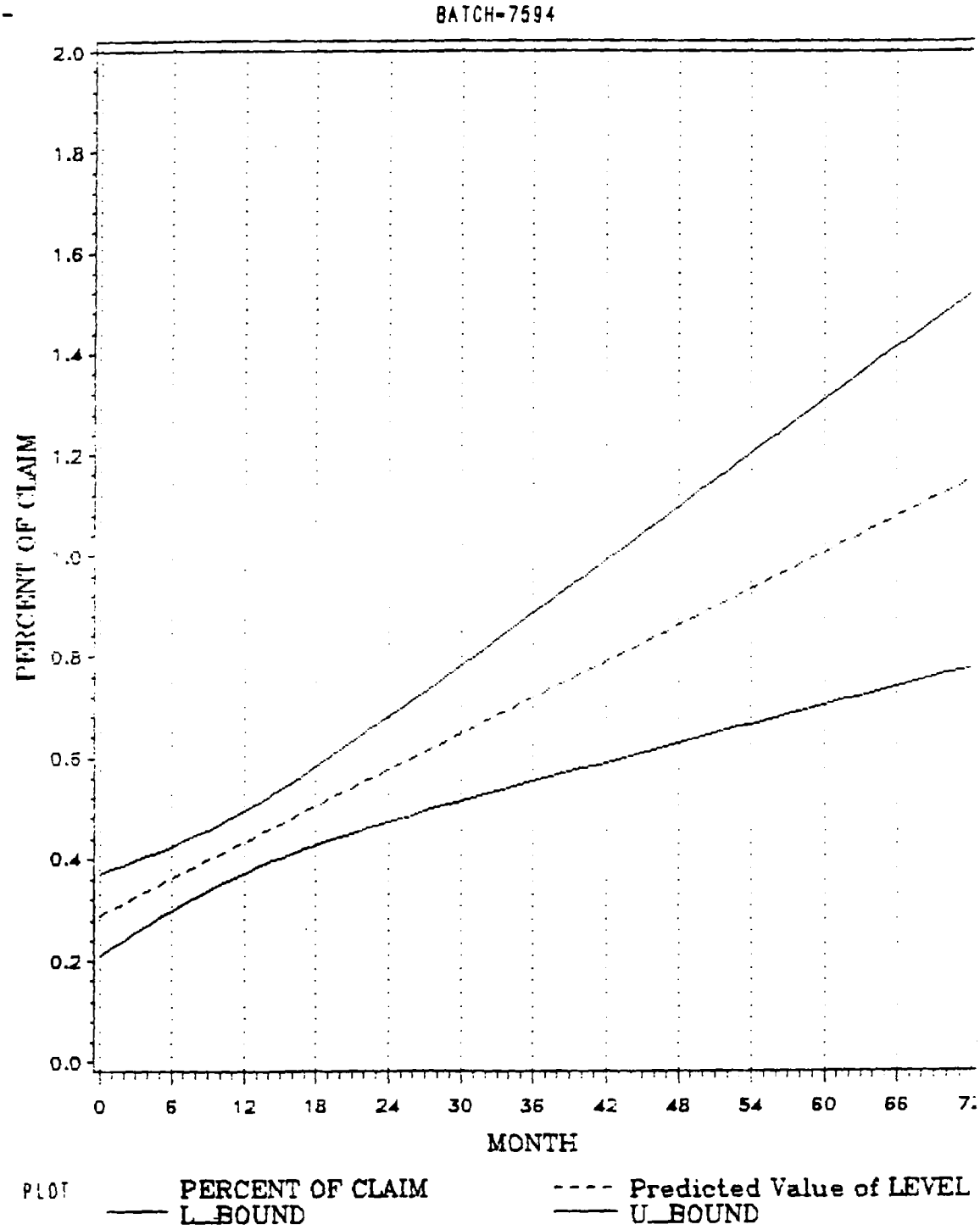


Figure 4
Package Type VI
Room Temperature 30° C



Appendix I

Model 1a (Package Type I)
Detecting The Slope Effect of Factor Manufacturer

Level = MNFCTR BATCH(MNFCTR) AGE AGE*MNFCTR AGE*BATCH(MNFCTR)

Model 1b (Package Type I)
Detecting The Intercept Effect of Factor Manufacturer

Level = MNFCTR BATCH(MNFCTR) AGE

Level = Variable For Degradation Data,

MATL = Variable For MATERIAL,

BATCH = Variable For Batch.

AGE = age in months, a covariate.

Appendix II

Model 1a (Package Type III)
Detecting The Slope Effect of Factor Material

Level = MATL BATCH(MATL) AGE AGE*MATL AGE*BATCH(MATL)

Model 2b (Package Type III)
Detecting The Intercept Effect of Factor Material

Level = MATL BATCH(MATL) AGE AGE*BATCH(MATL)

Level = Variable For Degradation Data,

MATL = Variable For MATERIAL,

BATCH = Variable For Batch.

AGE = age in months, a covariate.

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