CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-744

# STATISTICAL REVIEW(S)

# Statistical Review and Evaluation
# Chemistry

Date: November 1, 1999

NDA: 20-744

Applicant: Chiesi Pharmaceutici A.P.A.

Drug Name: Curosurf (poractant alfa) Intratracheal Suspension

Document Reviewed: Review of the acceptance limits used in the in-vivo quality control test of Curosurf, Ammendment to Report No. DF/96/194, November 11, 1998.

## Introduction

The proposed specifications for batch release based on in-vivo assessment of tidal volume , Vt, and Thorax-lung compliance, ©, in premature rabbit fetuses were developed based on the 5 batches in the Karolinska group that were not used in phase 3 clinical trials. The sponsor wants to demonstrate in this study that the data from the 15 batches in the clinical group and the 60 batches in the global group are not significantly different from the data in the Karolinska group. Thus the previously developed specifications can still be used for the release of subsequently produced batches of the drug product.

In the previous statistical analysis, the sponsor used the analysis of variance procedure to test the hypothesis that the Vt and © data (both conducted at 5 and 30 minutes) were not statistically significant among the three groups. However, in the sponsor's previous analysis, data of several batches were included in more than one of the three groups. The repeated use data of those batches violated the independence assumption of batches in the three groups.

## Sponsor's new analyses

In this new analysis, the sponsor corrected the above problem in the univariate and multivariate analyses of variance. The sponsor conducted two sets of analysis in this amendment. The first set included the tests by the univariate and multivariate analysis of variance that the Vt and © data are the same among the three groups of batches. The second set included the same types of analysis as the first set, but compared the batches in the Karolinska group versus the pooled batches of the clinical and global groups.

The sponsor indicated in his report that all the tests in the two sets of analysis did not show any statistical significance in Vt and © (both conducted at 5 and 30 minutes)

among the three groups or between the Karolinska group and the clinical-global pooled group. The sponsor then concluded at the end of his report that the acceptance limits used in the in-vivo activity quality control test are still reliable.

**Reviewer's Comments**

The sponsor has corrected the above mistake of including data of some batches in more than one of the three groups made in his previous analysis. The sponsor excluded from the clinical group two batches that were included in the Karolinska group, and from the global group all the batches that were included in the clinical group.

The statistical procedures, i.e., the univariate and the multivariate analyses of vairance, for testing the similarity of data in the three groups or between the Karolinska group and the clinical-global combined group are appropriate. The results from the analyses are valid with the assumption that the batches within each group are homogeneous.

The statistically significant TIDAL*GROUP and COMPLIANCE*GROUP interactions in the three-group analysis of variance are probably due to the large number of observations used in the analyses and probably can be ignored. The plots of changes from 5 minutes to 30 minutes in Vt and © show very little differences among the data in the three groups.

The average numbers of fetuses used in the three groups are different. They are 12.4 (62/5), 10.87 (163/15), and 10.1 (606/60) fetuses, respectively, for the Karolinska, Clinical, and Global groups. The sponsor did not give explanations for the differences. However, the differences should not invalidate the analyses and results purely from statistical consideration.

/S/

Karl K. Lin, Ph.D.
Expert Mathematical Statistician

APPEARS THIS WAY
ON ORIGINAL

Concur: /S/

S. Edward Nevius, Ph.D.
Director
Division of Biometrics II

cc: NDA 20-744 File
HFD-715/SENevius, SWilson, KKLin
HFD-715/Division Chronic File

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**Addendum to review dated August 10, 1998** AUG 2 0 1998
**Statistical consult**

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|---|---|
| NDA#: | NDA 20-744 |
| Date of consult request: | June 19, 1998 |
| Date of document | February 19, 1997 |
| Date of review: | August 6, 1998 |
| Applicant: | Dey Laboratories |
| Name of Drug: | Curosurf |
| Reviewer: | Girish Aras Ph.D. |

**Background:** This is in response to a consult requested by Dr. Joseph Sun. The applicant proposed *in vivo* (premature rabbit) testing as a routine release and stability test for the drug product. Also, this method was used for the testing of clinical batches and NDA stability batches. Dr. Sun requested verification of sponsor's calculations of the analysis of variance procedure applied to Tidal Volume values (Vt) and for Lung Thorax Compliance values ( C ) recorded during the ventilation sequence under Curosurf treatment.

**Reviewer's comments:** Statistical methodology employed by the sponsor is essentially correct. However, some batches are common to 'Karolinska group', 'clinical group' and 'global group'. The sponsor should perform the same calculations as in the original submission without repeating the batches so that statistical independence of the batches used in three groups will be maintained. For example, batch 9111011 is used clinical as well as global group and 'May87' is used in Karolinska and clinical groups. Analysis of variance should then be performed to conclude that there is no statistical difference within three batches as far as variables Vt and C are concerned.

Following comment should be included in the action letter:
Regarding the statistical analysis *of in vivo* testing in premature rabbits, the following revisions are requested.

a) Analysis of variance should be performed on the variables Tidal Volume (Vt) and Lung Thorax Compliance ( C ) for three groups of batches (Karolinska, clinical and global) reported in Tables 3. The groups should be reorganized so that the batches in each group are different, i.e. each batch should appear only in one group. This is necessary since validity of analysis of variance methodology requires statistical independence of the groups.
b) Analysis of a pooled group that includes all batches should also be performed and compared to the results obtained from each of the three groups to support the proposed acceptance criteria.

/S/ 8/26/1998

Girish Aras, Ph.D.
Mathematical Statistician

Concur: SWILSON /S/ 8/20/1998

cc:
Archival NDA 20-744
HFD-570/ENASHED
HFD-570/JSUN
HFD-570/SWILSON
HFD-570/DTOYER
HFD-715/divisional file

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AUG 10 1998

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Girish Aras, Ph.D.
Mathematical Statistician

Concur: /S/ 8/10/98 SWILSON

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