020-839__S-001

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER(S)

NDA 20-839/S-001

Trade Name: Plavix Tablets

Generic Name(s): (clopidogrel bisulfate)

Sponsor: Sanofi-Synthelabo, Inc.
Agent:

Approval Date: May 12, 1998

Indication: Provides for expiry date

MAY 12 1998

NDA 20-839/ S-001

5-12-98

Sanofi Pharmaceuticals, Inc.
Attention: Gregory M. Torre, Ph.D., J.D.
90 Park Avenue
New York, NY 10016

Dear Dr. Torre:

Please refer to your November 21, 1997 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plavix (clopidogrel bisulfate) Tablets, 75 mg.

The user fee goal date is May 24, 1998.

The supplemental application provides for a 36 month expiry date based on statistical analyses of [ ] stability data.

We have completed the review of this supplemental application and it is approved.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

Sincerely yours,

/S/ 5-12-98

Kasturi Srinivasachar, Ph.D.
Chemistry Team Leader, DNDC I
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc: NDA 20-839/ S-001
HFD-110/ DIV FILE
HFD-110/ JShort 5/11/98
HFD-110/ Project Manager/ DRoeder
HFD-92
DISTRICT OFFICE
HFD-810, CHoiberg
cg 05/11/98

Approval Date: November 17, 1997

APPROVAL

MAY 1 2 1998

CHEMIST'S REVIEW	1. ORGANIZATION HFD-110	2. NDA Number 20-839
3. Name and Address of Applicant (City & State) Sanofi Pharmaceuticals, Inc. New York, NY		4. Supplement(s) Number(s) Date(s) SCM-001 21 Nov 97
5. Drug Name Plavix	6. Nonproprietary Name Clopidogrel bisulfate	7. Amendments & Other (reports, etc) - Dates
8. Supplement Provides For: Stability data to support a 36 month expiry date for Plavix tablets.		
9. Pharmacological Category Prevention of vascular ischemia	10. How Dispensed [X] Rx [ ] OTC	11. Related IND(s)/ NDA(s)/DMF(s)
12. Dosage Form(s) TCM	13. Potency(ies) 75 mg	
14. Chemical Name and Structure		15. Records/Reports Current [X] Yes [ ] No Reviewed [X] Yes [ ] No

16. Comments

The firm provides [ ] stability data at 25°C/60%RH for [ ] batches of tablets packaged in three configuration. SAS analyses are provided. A consult request was sent to Biometrics requesting a review of the firm's statistical data. A review, dated 17 Apr 98, was received from Dr. K. Mahjoob, in which he concluded that the requested 36 month expiry date was justified on the basis of the data presented. The report has been submitted to the archival jacket and division file.

(continued)

17. Conclusions and Recommendations

The 36 month expiry date for the drug product is justified on the basis of the data presented.

APPROVAL is recommended.

18. REVIEWER

Name James H. Short [S]

Date Completed 28 Apr 98

Distribution: [ ] Original Jacket [ ] Reviewer [ ] Division File [ ] CSO

jhs/4/27/98/N20-839.S01

S 5.4.98

16. Comments: (continued)

The firm has provided stability data for Plavix Tablets, 75 mg, as summarized below.

Lot No.	Package	Condition	Test Points, mos
M248M	Blisters 90s 500s	25°C/60%RH	
M249M	Blisters 90s 500s	25°C/60%RH	
M250M	Blisters 90s 500s	25°C/60%RH	

At each time point the tablets were assayed for potency, dissolution and impurities [redacted]. A summary table of the results follows.

Table 4.1: EDs for Clopidogrel Tablets at [ ] at 25°C/60%RH

Characteristic	Package	Batch	Estimated Intercept	Estimated Slope	ED (months)
Potency	P/2	M248M			36+
		M249M			36+
		M250M			36+
	P/10	All			36+
	P/7	All			36+
Dissolution	P/2	M248M			36+
		M249M			36+
		M250M			36+
	P/10	M248M			36+
		M249M			36+
		M250M			36+
	P/7	M248M			36+
		M249M			36+
		M250M			36+
[ ]	P/2	M248M			36+
		M249M			36+
		M250M			36+
	P/10	M248M			36+
		M249M			36+
		M250M			36+
	P/7	M248M			36+
		M249M			36+
		M250M			36+
[ ]	P/2	M248M			36+
		M249M			36+
		M250M			36+
	P/10	All			36+
	P/7	M248M			36+
		M249M			36+
		M250M			36+

The firm also presents graphical representation of the data. From the graphs it is obvious that all parameters stay well within specifications out to 36 months.

Statistical Review and Evaluation
Stability Review of PLAVIX

DATE: APR 17 1998

NDA #: 20-~~895~~ 839 (REF No. 001; Supplement for SCE).

DATE RECEIVED BY CDER: November 24, 1997.

DATE OF REQUEST FOR REVIEW: April 06, 1998.

APPLICANT: Sanofi Pharmaceuticals.

NAME OF DRUG: Clopidogrel Bisulfate (PLAVIX®) 75 mg Tablets.

DOCUMENTS REVIEWED: Stability Data.

The review of the stability submission of PLAVIX is requested by Dr. James Short, the Chemistry Team Leader from the Division of Cardio Renal Drug Products (HFD-110).

Introduction

The stability supplement of PLAVIX contains the data of [ ] studies of 75 mg tablets with respect to **potency** (in percent of label claim), **dissolution** and the level of **impurities** to support a claim of 36 months Expiration Dating Period.

The data are collected from three batches M248M, M249M and M250M in three different packages under the storage condition of 25° C and 60% RH.

The three packages are described in **Table 1**:

TABLE 1: Package Description

Package	Description
P/2	[ ] Blister
P/10	[ ] Bottle W/Desiccant
P/7	[ ] Bottle W/Desiccant

Statistical Reviewer: Kooros Mahjoob

The stability indicators and the limitations are described in **Table 2**:

TABLE 2: Stability Indicators and Limitations

Indicator	Description –
Potency	within
Dissolution	Q + —
Impurities	Not exceeding –

The objective of the analysis is to establish the expiration dating period of 36 months.

Statistical Method

The sponsor has used the SAS Stability Program, developed by the FDA's statistician (1992). The procedures are as follows:

1. For each stability indicator, the program first examines the poolability of data across the three batches and pools the data if they are poolable.

2. Next, the program fits a straight regression line to stability observations as a function of time. The fitted line is called "Mean Degradation Curve". The program uses the pooled data, if they were poolable, or else, the data of the individual batches and computes the **lower** and **upper** 100(1- α)% confidence bound of the fitted lines. Then, the estimate of the expiration time is the earlier of the two times when either the lower 100(1- α)% confidence bound intersects with the lower specification limit or the upper 100(1- α)% confidence bound intersects the upper specification limit. The readers may consult the figures (copied from the submission) in Appendix A.

The sponsor has used one-sided 95% lower bound for potency and dissolution for the reason that "the potency and dissolution are expected to decrease with time" and has used one-sided 95% upper bound for impurity.

Sponsor's Results

The sponsor results are summarized in **Table A.1** of **Appendix A**. The table contains the information on intercepts and slopes of the fitted regression lines (Mean Degradation Curves), and the last column presents the estimate of the expiration dating period, for all batches. As indicated, the expiration dating period is beyond the 36 months claimed, for all batches.

The Reviewer's Comments and Conclusion

In the FDA's standard stability analysis, the statisticians do not make any assumption as to whether potency/dissolution are expected to increase or decrease with time. Chemical parameters which only degrade in theory can still manifest positive slope estimates. Therefore, the estimate of the expiration dating period is the earlier of the two times when either the lower of the two-sided 95% confidence bound intersects with the lower specification limit or the upper confidence bound intersects with the upper specification limit. As can be seen from the attached table (Appendix A), for dissolution, the estimates of the slopes are positive numbers (although they may not be statistically significantly different from zero). However, as the concern is for passing a minimal level , — , the lower confidence bound is the crucial one. Similarly, with impurities, the upper confidence bound is of importance. For chemical parameters with only one specification limit, a one-sided 95 % confidence bound is used.

It should be mentioned that, if there is a justification to use a one-side confidence bound, rather than two-sided bounds, then the confidence limit should be — rather than 95%.

Conclusion: At any rate, by examination of the fitted lines (see the figures in Appendix A), it appears that, even with the use of — confidence bounds, the results strongly support the claim of a 36-month expiration dating period. However, this time is extrapolated for more than 6 months (12 months) beyond the actual data.

/S/

Kooros Mahjoob, Ph.D.
Mathematical Statistician

This review consists of 3 pages and Appendix A consisting of 13 pages.

Concur: Dr. Chi /S/

CC:

20-839
Arch. NDA ~~20-893~~ (PLAVIX)

HFD-110
HFD-110/Dr. Short
HFD-110/Mr. Roeder
HFD-344/Dr. Barton
HFD-700/Dr. Fairweather
HFD-710/Dr. Chi
HFD-710/Dr. Mahjoob
HFD-710/Chron.

K. Mahjoob: 4-5301:Biometrics 1/Team 1:km.

Statistical Reviewer: Kooros Mahjoob

APPENDIX A

NDA 20-839: PLAVIX
Stability Review

Table 4.1: EDs for Clopidogrel Tablets at ___ at 25°C/60%RH

Characteristic	Package	Batch	Estimated Intercept	Estimated Slope	ED (months)
Potency	P/2	M248M			36+
		M249M			36+
		M250M			36+
	P/10	All			36+
	P/7	All			36+
Dissolution	P/2	M248M			36+
		M249M			36+
		M250M			36+
	P/10	M248M			36+
		M249M			36+
		M250M			36+
	P/7	M248M			36+
		M249M			36+
		M250M			36+
___	P/2	M248M			36+
		M249M			36+
		M250M			36+
	P/10	M248M			36+
		M249M			36+
		M250M			36+
	P/7	M248M			36+
		M249M			36+
		M250M			36+
___	P/2	M248M			36+
		M249M			36+
		M250M			36+
	P/10	All			36+
	P/7	M248M			36+
		M249M			36+
		M250M			36+

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page(s) of trade secret and/or confidential commercial information

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